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# ORGANIC CHEMISTRY

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## PREFACE

This book is the result of an attempt on the part of the authors to record the substance of Chemistry 34 and Chemistry 36 as they are given at the University of Illinois. Chemistry 34 is for beginners and embraces the entire field, being designed primarily to familiarize the student with the principal types of organic compounds. Part I (Chapters I to XVIII, inclusive) presents the subject matter of this course. Chemistry 36 covers much the same ground as Chemistry 34, but from a more mature viewpoint and with particular emphasis on the use of organic reactions in synthesis. Part II (Chapters XIX to XXXIV) contains the material offered in this course. Together, these courses constitute a year of work in organic chemistry for beginners. Part II has also been used extensively here and elsewhere by graduate students in connection with survey courses and in preparation for Ph.D. examinations. Probably the chief advantage gained by covering the entire subject in each course is due to the repetition which this method involves. In this book the amount of repetition is, for obvious reasons, considerably less than that employed in the classroom. Such details of presentation are left to the teacher.

The general arrangement of the material and the style of presentation are traditional in the department. The only features that are in any sense new and hence not amply tested in the classroom relate to the reports of new developments in the field.

The authors recognize that any credit for the present version belongs in a large degree to their colleagues who have contributed to the development of the courses, the contents of which it purports to reproduce. Foremost among these is Professor C. S. Marvel who was in charge of these courses for many years.

REYNOLD C. FUSON  
H. R. SNYDER



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## PART I

### CHAPTER I

#### INTRODUCTION

In the early development of the science of chemistry attention was devoted largely to the acids, bases, and salts. These substances probably were selected because they are soluble in water and most of their reactions are rapid. From the study of these and other compounds the laws governing the combination of the elements were gradually elucidated. However, during this period a very large group of compounds, those present in or obtained from living organisms, was set apart. It was believed that the formation of these so-called *organic* substances could be brought about only in the living plant or animal, and that organic materials could not be treated according to the concepts employed with *inorganic* compounds.

The first of these beliefs was shattered in 1824 when the German chemist Wöhler found that the typical inorganic salt, ammonium cyanate, could be converted easily to the typical organic compound, urea. This demonstration that an organic compound could be synthesized apart from any complex life process thus destroyed the major distinction between inorganic and organic chemistry. Further investigations of organic compounds soon showed that these materials are governed by the same fundamental laws which apply to inorganic substances, and that the real distinction between the two types is that organic materials usually contain both carbon and hydrogen whereas inorganic substances usually do not. The separation of the two fields has been maintained because of the tremendous number of organic compounds, there being several times as many known compounds of carbon as there are of all other elements.

The picture called to the mind of the well-informed man by the words organic chemistry is not one focused on a vast array of carbon compounds. Rather it is a practical, everyday picture of the innumerable articles which he manufactures, buys, sells, and uses. The mere mention of synthetic fabrics, the treatment of leathers, the manufacture of dyes, soaps, and new detergents, the production of better gasolines, oils, and



automobile tires, more enduring paints, new medicines, or cosmetics, brings to mind the extensive fields which organic chemistry has entered. It is no longer news that organic chemistry is an inseparable part of the industries and arts of present-day life.

## SUGGESTED READING

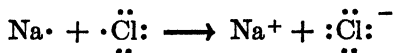
WARREN, "Contemporary Reception of Wöhler's Discovery of the Synthesis of Urea," *J. Chem. Education*, **5**, 1539 (1928).

## CHAPTER II

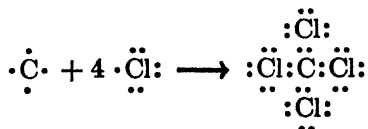
### THE STRUCTURE OF MOLECULES

The property of carbon which distinguishes it most conspicuously is its tendency to form non-ionizing links, both with other carbon atoms and with atoms of different elements. In other words, the type of union most frequently encountered in the carbon compounds is the covalent bond, whereas the polar or electrovalent bond may be considered typical of the inorganic compounds. The differences between these two kinds of valence may be seen by examination of examples.

The formation of sodium chloride from the elements illustrates the simplest mode of formation of an electrovalent bond. The sodium atom has one electron (Group I of the periodic table) in its valence shell. Beneath this valence electron lies a complete shell of eight electrons. The chlorine atom has an outer shell of seven electrons (Group VII of the periodic table). When these two atoms react, the electron simply passes from the sodium atom to the chlorine atom so that both resulting particles have outer shells of eight electrons. The sodium atom, by losing the negatively charged electron, becomes the positive sodium ion. The chlorine atom, by gaining the electron, becomes the negative chloride ion. There is actually no bond between the two ions. They attract each other, by virtue of their opposite charges, but an individual sodium ion will be attracted by any negative ion which happens to be near it, and not solely by the particular chloride ion to which it originally yielded its electron. The following equation represents the formation of sodium chloride from the elements.



The formation of carbon tetrachloride from carbon and chlorine involves a process of a different type. The carbon atom (Group IV of the periodic table) has four electrons in its valence shell. When it reacts with a chlorine atom it contributes one electron, and the chlorine contributes one, to the formation of a pair held jointly by the two atoms. By combining with four chlorine atoms, the carbon atom acquires a shell of eight electrons, as follows:

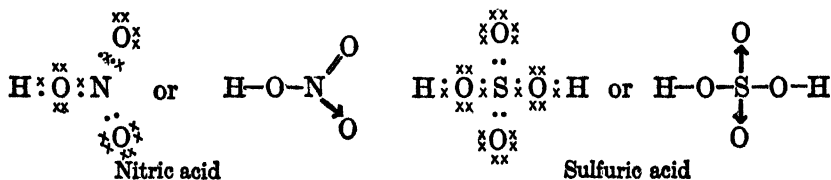


As indicated in the formula there is no actual transfer of electrons here, but rather a sharing in such a way that each atom is able to complete its octet. The result is a *fixed* bond between the carbon atom and the chlorine atom.

A comparison of the properties of sodium chloride and carbon tetrachloride illustrates the differences between ionic compounds and covalent compounds. For instance, sodium chloride is high-melting and non-volatile. It is soluble in water. Its reactions, being the reactions of the sodium ion and the chloride ion, are extremely rapid. Carbon tetrachloride, on the other hand, is a volatile liquid. It is insoluble in water. Most of its reactions are extremely slow in comparison with those of sodium chloride. Thus, sodium chloride reacts instantly with silver nitrate to give a precipitate of silver chloride, but under ordinary conditions carbon tetrachloride does not react at all with silver nitrate. This shows that each chlorine atom is firmly attached to the carbon atom and that no chloride ions are present.

It is not to be concluded from the foregoing discussion that inorganic compounds contain only ionic or electrovalent bonds, nor that all links in all organic compounds are covalent bonds. Actually, many inorganic compounds contain covalent bonds, and many organic substances have one or more electrovalent linkages.

A third type of valence, known as the *coordinate covalence*, also occurs in both organic and inorganic materials. It consists of a shared pair of electrons, both of which are contributed by one of the atoms. It is present in such common reagents as sulfuric acid and nitric acid. In the formulas below the electrons originally belonging to the nitrogen, sulfur, and hydrogen atoms are indicated by dots, while those of the oxygen atoms are represented by crosses.



It will be noted that in these formulas the nitrogen and sulfur atoms have complete octets. One of the oxygen atoms in nitric acid has achieved this state by sharing the *pair* furnished by the nitrogen atom. In sulfuric acid two oxygen atoms are held in this manner. Formulas of this kind are usually abbreviated as shown, an arrow indicating the coordinate covalent link. The arrow points from the *donor* to the *acceptor* of the electron pair. The coordinate covalent link is sometimes called the

semipolar bond. The origin of this term becomes clear from a consideration of the nitrogen-oxygen coordination bond in nitric acid. Since it still has all its original six electrons plus an interest in the pair which holds it to the nitrogen, the oxygen must have a negative charge. The nitrogen, on the other hand, since it has given up a share of the pair to the oxygen atom without gaining any interest in the latter's electrons, must bear a positive charge.

The carbon atom forms covalent links not only with chlorine, but with a great variety of elements, including the other halogens, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and occasionally other elements. Most striking of all is the formation of stable covalent bonds with other carbon atoms. Thus, organic compounds may contain carbon atoms in *chains* of two, three, four, or more. In fact, there is no known limit to the number of carbon atoms which may be united in this way. When this is considered, together with the various elements mentioned which may be united with the carbon atoms in these chains, it becomes evident that the number of possible organic compounds is extremely large. In addition, as a consequence of the fixed character of a covalent bond, it is often possible to obtain many different compounds from the same group of atoms by varying the *arrangement* of the atoms within the molecule. Such compounds are said to be *isomers*; the phenomenon, known as *isomerism*, is very common among organic compounds.

Because of the formation of carbon chains and the existence of isomers, there is no mathematical limit to the number of possible carbon compounds. The successful treatment of organic chemistry must, therefore, depend upon the classification of the compounds into broad groups of related substances. A very satisfactory classification is that based on *structure*. By structure is meant the manner of attachment of the various atoms which make up a particular compound. For example, carbon atoms can be joined by one, two, or three bonds, giving rise to three different species of compounds. Carbon forms stable single, double, and triple bonds with nitrogen also. Moreover, it may be joined to sulfur, the halogens, and many other elements.

As a result of the remarkable and varied capacity of carbon for combining with itself and with other elements, many different types of organic compounds are possible. Each type or class is characterized by a particular group known as its *functional group*. A few of the principal functional groups and the classes of compounds to which they give rise are shown in Table I.

Of the dozens of classes of organic compounds, the basic type is that composed of *hydrocarbons*, compounds containing only hydrogen and carbon. Since the hydrocarbons furnish the foundations upon which

all other types of organic compounds are built, it is desirable to consider them first.

TABLE I  
SOME SIMPLE FUNCTIONAL GROUPS

Class of Compound	Functional Group	
	Formula	Name
Alcohols	-OH	Hydroxyl group
Acids	$\begin{array}{c} \text{O} \\ \diagup \\ -\text{C}-\text{OH} \end{array}$	Carboxyl group
Aldehydes and ketones	$\begin{array}{c} \text{O} \\ >\text{C}=\text{O} \end{array}$	Carbonyl group
Amines	-NH <sub>2</sub>	Amino group
Mercaptans	-SH	Sulfhydryl group
Nitro compounds	-NO <sub>2</sub>	Nitro group
Sulfonic acids	-SO <sub>3</sub> H	Sulfonic acid group

## CHAPTER III

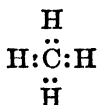
### SATURATED HYDROCARBONS

#### Methane

The hydrocarbons can be grouped into various classes on the basis of their chemical reactions. Those called *saturated* hydrocarbons have been so named because of their relative inertness. The name *paraffin* (too little affinity) carries the same connotation.

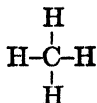
The simplest of the paraffin hydrocarbons is methane,  $\text{CH}_4$ . It is the chief constituent of natural gas, and as such occurs in large quantities. It has been called *marsh gas* because of its formation during the anaerobic fermentation of vegetable matter beneath the stagnant water of swamps. Methane usually occurs along with coal, and because it forms an explosive mixture ("fire damp") with air, its presence constitutes one of the hazards of mining.

Since carbon has a valence of four, it is obvious that each of the hydrogen atoms in the methane molecule must be attached directly to the carbon atom. The bonds are covalent, so the formula may be written as follows:



Electronic formula of methane

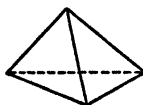
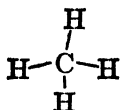
In practice, formulas of this type are used only when it is necessary to call particular attention to the electrons of the bonds. For convenience the links are usually represented by lines. Each line in the formula below is, then, to be considered as an abbreviation indicating a pair of electrons shared between the two atoms which it joins.



Structural formula of methane

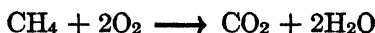
This structural formula fails to represent correctly the distribution in space of the atoms in the methane molecule. It is known that the

four pairs of electrons about a carbon atom arrange themselves so that each pair is at the greatest possible distance from each of the other pairs. The result is that the four valences are directed in such a way that the four attached groups bear the same spatial relation to each other as do the four points of a regular tetrahedron. An accurate representation of the methane molecule must, then, involve a three-dimensional drawing.

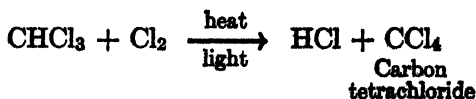
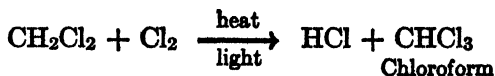
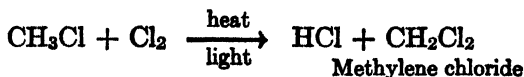
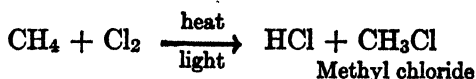


Because of this distribution of valences, carbon is often referred to as a *tetrahedral* atom. It will become apparent later that the spatial relationship of the groups about a carbon atom may have a profound influence on the properties of a compound. However, because they are difficult to draw, the three-dimensional formulas are used only when they are necessary.

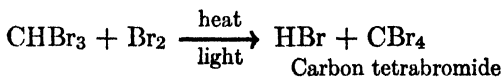
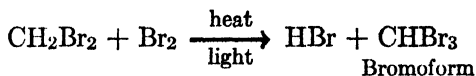
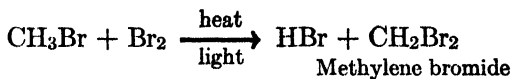
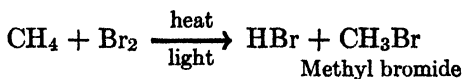
Although the paraffins are the least reactive of the hydrocarbons, they do nevertheless undergo a variety of transformations under the influence of appropriate reagents. Thus, whereas it resists the action of mild oxidizing agents such as aqueous solutions of potassium permanganate, methane is readily oxidized when heated sufficiently with oxygen. This, of course, is the reaction which takes place when natural gas is burned.



Chlorine attacks methane, but only at elevated temperatures or in the presence of ultraviolet light. The reaction involves the removal of hydrogen atoms, their places being taken by chlorine atoms.

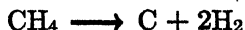


The reaction is of the type known as a *substitution*. By substitution is meant the direct replacement of hydrogen by other atoms. A similar substitution occurs when bromine is used.



Iodine, the least reactive of the halogens, does not react with methane. However, the iodine derivatives of methane, methyl iodide, methylene iodide, iodoform, and carbon tetraiodide, can be obtained by other methods. Fluorine is so extremely reactive that direct fluorination is seldom used. In fact, neither the chlorination nor the bromination of methane is easily controlled. Because the rates of chlorination of methane, methyl chloride, methylene chloride, and chloroform are nearly identical, an attempt to prepare any one of the chlorine derivatives results in a mixture containing all four of them in addition to unchanged methane. Other methods which give the individual derivatives are therefore more convenient for laboratory preparations.

Like nearly all organic compounds, methane decomposes under the influence of extreme heat. The products are carbon and hydrogen.



This reaction is used in the preparation of lampblack from natural gas. A simple way of effecting it is to burn methane with a limited quantity of air. The heat of the flame causes the decomposition of the methane which is in excess of the oxygen present. Thermal decomposition of organic compounds is usually referred to as *pyrolysis*. When a hydrocarbon is concerned, the reaction is sometimes called *cracking*.

### The Higher Paraffins

Methane is the simplest member of a series of hydrocarbons of very similar chemical characteristics. The next higher member is ethane ( $\text{C}_2\text{H}_6$ ) and following ethane are propane ( $\text{C}_3\text{H}_8$ ) and butane ( $\text{C}_4\text{H}_{10}$ ). These compounds may be represented by the general formula  $\text{C}_n\text{H}_{2n+2}$



in which  $n$  is the number of carbon atoms. The formulas and boiling points of a number of them are given in Table II. It will be seen that the formula of any member can be obtained by adding  $\text{CH}_2$  to that of the preceding member. Such a series of compounds is known as a *homologous series*. A homologous series may be defined as a group of structurally similar compounds, each member of which differs from the preceding member by  $\text{CH}_2$ . The concept of homology is one of the fundamentals of organic chemistry.

TABLE II  
STRAIGHT-CHAIN SATURATED HYDROCARBONS

Name	Boiling Point	Formula	Structural Formula
Methane	-161°	$\text{CH}_4$	$\text{CH}_4$
Ethane	-88	$\text{C}_2\text{H}_6$	$\text{CH}_3\text{CH}_3$
Propane	-45	$\text{C}_3\text{H}_8$	$\text{CH}_3\text{CH}_2\text{CH}_3$
Butane	0	$\text{C}_4\text{H}_{10}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$
Pentane	36	$\text{C}_5\text{H}_{12}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
Hexane	69	$\text{C}_6\text{H}_{14}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
Heptane	98	$\text{C}_7\text{H}_{16}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
Octane	125	$\text{C}_8\text{H}_{18}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
Nonane	151	$\text{C}_9\text{H}_{20}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
Decane	174	$\text{C}_{10}\text{H}_{22}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

Only one carbon skeleton can be written for each of the hydrocarbons up to and including propane. However, in the formula,  $\text{C}_4\text{H}_{10}$ , the carbons may be arranged either in a *straight chain*,  $\begin{array}{c} | & | & | & | \\ -\text{C}-\text{C}-\text{C}-\text{C}- \\ | & | & | & | \end{array}$ , or in

a *branched chain*,  $\begin{array}{c} | & | & | \\ -\text{C}-\text{C}-\text{C}- \\ | & | & | \\ | & & \\ -\text{C}- \\ | \end{array}$ . Actually two different butanes, called

normal butane (*n*-butane) and isobutane, are known:



*n*-Butane

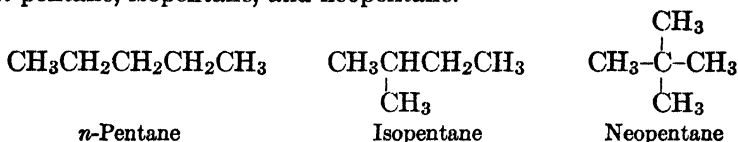


Isobutane

These compounds have entirely different physical properties. For instance, the boiling point of isobutane ( $-10^\circ$ ) differs by ten degrees from that of *n*-butane ( $0^\circ$ ). It will be seen later that there are also differences in their chemical properties.

Butane and isobutane are *isomers* of each other. *Isomerism* may be defined as the existence of two or more compounds of the same molecular formula, but of different structures.

In a similar manner it is possible to write three structures for the formula,  $C_5H_{12}$ , and, in fact, three isomeric pentanes are known. They are *n*-pentane, isopentane, and neopentane.



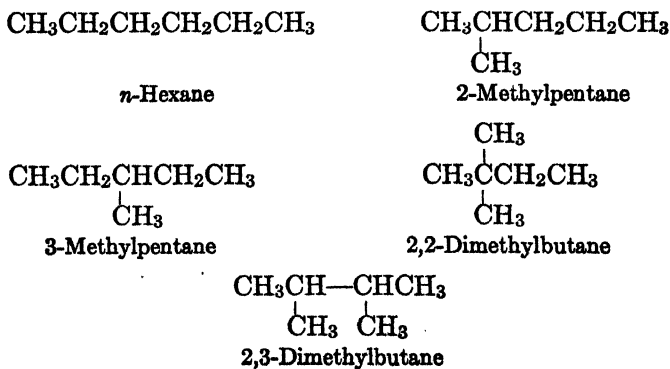
The number of possible isomers increases rapidly as the number of carbon atoms in the hydrocarbon molecule is increased. Thus, there are five hexanes, nine heptanes, eighteen octanes, and thirty-five nonanes. The method used above for naming the isomeric butanes and pentanes would become extremely cumbersome if an attempt were made to extend it to larger molecules. For this reason a simple system of naming such organic compounds was devised by a group of chemists meeting in Geneva in 1894. The following are the principles of the *Geneva system of nomenclature*.

1. A compound is named as a derivative of the hydrocarbon corresponding to the longest carbon chain present in the molecule. The name of this hydrocarbon serves as the stem of the name of the compound.

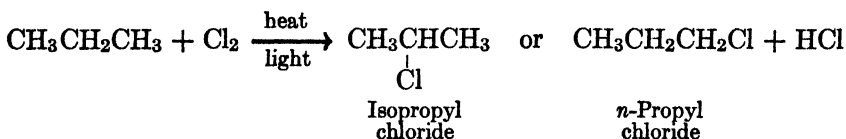
2. The type of the compound, that is, the homologous series to which it belongs, is indicated by a suffix. For the paraffins this suffix is *ane*.

3. Groups attached to the carbon chain are indicated by suitable prefixes. In order to specify the location of these groups the carbon chain is numbered in such a way that the numbers used in the name are the smallest possible.

The use of these rules is illustrated by the names of the five hexanes. The  $CH_3$  group is known as the methyl group.

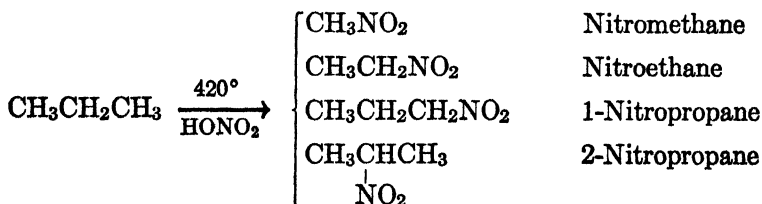


The paraffin hydrocarbons resemble methane in their chemical properties. They resist the action of chemical oxidizing agents such as aqueous potassium permanganate. They react with chlorine and bromine at high temperatures or in the presence of strong ultraviolet radiation. The reaction, like that of methane, is one of substitution.

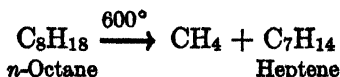


The introduction of a single chlorine atom into the propane molecule gives rise to two isomers, isopropyl chloride and *n*-propyl chloride. With the higher hydrocarbons, the number of monochloro derivatives increases rapidly. The production of isomers which are not easily separated, together with further chlorination of part of the monochloro derivatives, limits the usefulness of this reaction. However, the chlorination of a mixture of the pentanes is operated as a commercial process for preparing materials used as solvents (p. 230).

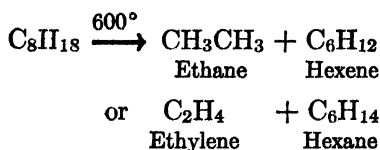
The paraffins undergo nitration, but only at elevated temperatures; the reaction is accompanied by cleavage of the carbon chains. For instance, propane can be converted to a mixture of nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane.



Thermal decomposition, or cracking, converts the paraffins into hydrocarbons of lower molecular weight. Thus, when *n*-octane is heated to the temperature of 600° the reaction product consists of a mixture of *saturated* and *unsaturated* hydrocarbons having from one to eight carbon atoms. The decomposition involves the breaking of the carbon chain at random points. Cleavage at the end of the chain produces methane and the unsaturated hydrocarbon, heptene.

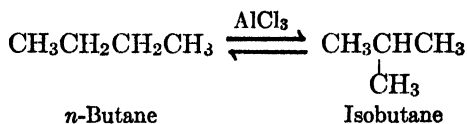


Cleavage at the second carbon of the chain may produce either ethane and hexene, or ethylene and hexane.



The decomposition appears to take place in all the possible ways, so that a variety of products is formed. Cracking is of extreme importance in the production of gasoline. It will be considered in greater detail in connection with petroleum (p. 29).

Certain catalysts are capable of *isomerizing* paraffin hydrocarbons. For instance, in contact with aluminum chloride, *n*-butane changes to an equilibrium mixture of *n*-butane and isobutane.

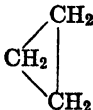
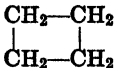
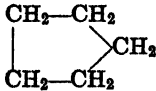
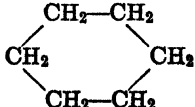


### The Cycloparaffins

The cycloparaffins correspond to the formula,  $\text{C}_n\text{H}_{2n}$ , yet have many of the properties of the paraffins. Their structures are characterized

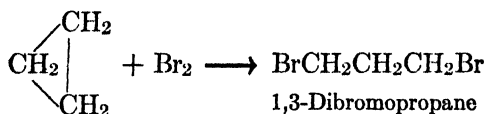
TABLE III

## CYCLOPARAFFINS

Name	Structural Formula	Boiling Point
Cyclopropane		-34.4°
Cyclobutane		13
Cyclopentane		49.5
Cyclohexane		81.4

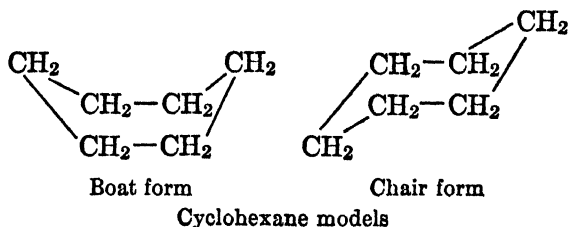
by the presence of carbon *rings*. The formulas and boiling points of some of the simpler cycloparaffins are given in Table III.

Cyclopropane is much more reactive than the open-chain paraffins. It absorbs bromine at room temperature and in the absence of light to give the open-chain dibromide, as shown by the following equation.



Cyclobutane is much less reactive toward bromine than is cyclopropane, and cyclopentane and cyclohexane cannot be distinguished from their straight-chain analogs by means of this reagent. The abnormal reactivity of cyclopropane and cyclobutane can be ascribed to the distortion of the carbon valences in the small rings. In cyclopropane the angle between any two valences in the ring is  $60^\circ$ , whereas the normal angle between carbon valences is  $109^\circ 28'$ . The compression of the valence angles in the small ring results in a *strain* within the molecule. In cyclobutane the angles are less highly compressed so that less strain and consequently less tendency toward ring opening exist. The angle of the regular pentagon is  $108^\circ$ , or almost identical with the tetrahedral angle. It follows, then, that cyclopentane should be practically free from strain and that its chemical behavior should approximate very closely that of *n*-pentane.

Cyclohexane is also free from strain; because all six carbons do not lie in the same plane, the normal valence angle need not be distorted. Two such models of cyclohexane can be constructed. They are called the *boat* and *chair* forms.



Since it has not been possible to separate two isomeric cyclohexanes, it is believed that the two forms are readily interconvertible.

Compounds containing cycloparaffin rings with more than thirty carbon atoms in the ring have been prepared and none of them exhibits any appreciable strain. This is to be expected from a study of models, for all such rings of six or more members can exist in non-planar, strainless forms (p. 351).

### The Relation of the Paraffin Hydrocarbons to Other Classes of Compounds

It has been mentioned that the various types of organic compounds are classified according to the *functional groups* (p. 5) which they contain. Most of the simple types may be regarded as *derivatives* of the paraffin hydrocarbons, the derivative differing from the parent hydrocarbon in having a functional group in place of one or more hydrogen atoms. For example, methyl chloride ( $\text{CH}_3\text{Cl}$ ) differs from methane ( $\text{CH}_4$ ) in having a chlorine atom in place of one hydrogen atom. The corresponding derivative of ethane is ethyl chloride ( $\text{CH}_3\text{CH}_2\text{Cl}$ ). Two such derivatives may be obtained from propane; they are *n*-propyl chloride (1-chloropropane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ ) and isopropyl chloride (2-chloropropane,  $\text{CH}_3\text{CH}(\text{Cl})\text{CH}_3$ ). These substances are the first members of



the homologous series of *alkyl chlorides*. The functional group of the series is the chlorine atom; it is attached to an *alkyl radical*, the radical obtained from a paraffin hydrocarbon by the removal of one hydrogen atom. The alkyl chlorides thus have the general formula  $\text{C}_n\text{H}_{2n+1}\text{Cl}$ . This formula is sometimes abbreviated as  $\text{RCl}$  ( $\text{R} = \text{C}_n\text{H}_{2n+1}$ ).

The alcohols form a similar series in which the functional group is the hydroxyl group. The first members are methyl alcohol ( $\text{CH}_3\text{OH}$ ), ethyl alcohol ( $\text{CH}_3\text{CH}_2\text{OH}$ ), and the isomeric propyl alcohols, *n*-propyl alcohol ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ ) and isopropyl alcohol ( $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$ ). They



conform to the general formula  $\text{C}_n\text{H}_{2n+1}\text{OH}$  ( $\text{ROH}$ ).

In most cases, a single functional group gives rise to only one homologous series. An interesting exception occurs in compounds containing the carbonyl group ( $\text{>C=O}$ ). The simple carbonyl compounds may be regarded as derived from paraffins by replacement of two hydrogen atoms with a doubly bound oxygen atom. If the carbon atom carrying this oxygen atom is located at the end of a carbon chain the substance

is an *aldehyde*. Examples are  $\text{HC} \begin{array}{c} \text{O} \\ // \\ \text{---} \end{array} \text{H}$  (formaldehyde),  $\text{CH}_3 \begin{array}{c} \text{O} \\ // \\ \text{---} \end{array} \text{H}$  (acetal-

dehyde), and  $\text{CH}_3\text{CH}_2 \begin{array}{c} \text{O} \\ // \\ \text{---} \end{array} \text{H}$  (propionaldehyde). When the carbonyl group is connected to two carbon atoms, that is, when it is located at some point other than an end of the carbon chain, the substance is a

*ketone*. The simplest ketone is  $\text{CH}_3 \begin{array}{c} \text{O} \\ // \\ \text{---} \end{array} \text{CH}_3$  (acetone). The aldehydes and ketones are considered to constitute separate homologous series because their reactions differ in some important respects. For example,

the aldehydes mentioned above are very easily oxidized to the corresponding acids ( $\text{HC}-\text{OH}$ , formic acid;  $\text{CH}_3\text{C}-\text{OH}$ , acetic acid; and  $\text{CH}_3\text{CH}_2\text{C}-\text{OH}$ , propionic acid), but the ketone is unaffected by mild oxidizing agents.

In the following chapters the properties conferred upon compounds by the various functional groups are considered in some detail. The classes most closely related structurally to the paraffins are those consisting of unsaturated hydrocarbons.

### PROBLEMS

1. Define and illustrate the following terms: isomers, homologs, substitution, chlorination, cracking, strainless rings.
2. Write structural formulas of the following compounds: 2,3,4-trimethylpentane, 2,2,3-trimethylbutane, 3-ethylpentane, 2,2,3,3-tetramethylbutane, cycloheptane, methylcyclohexane, 1,3-dimethylcyclopentane.
3. Compare the reactivity toward bromine of propane and cyclopropane; of *n*-hexane and cyclohexane. Write the formulas of all the monochloro derivatives of *n*-hexane; of cyclohexane; of methylcyclohexane.
4. Write the electronic formulas and abbreviated electronic formulas of the following compounds: ethane, ethyl chloride, ethyl alcohol, acetaldehyde, acetic acid, nitroethane.

### SUGGESTED READING

GABRIEL, "The Nitroparaffins," *Ind. Eng. Chem.*, **32**, 887 (1940).

## CHAPTER IV

### UNSATURATED HYDROCARBONS

#### The Olefins

The simplest unsaturated hydrocarbons are those of the general formula  $C_nH_{2n}$ . They are called olefins or, since ethylene is the first member of the series, ethylenic hydrocarbons. Ethylene has the formula  $C_2H_4$ . It can be shown that each of the carbon atoms is connected to two hydrogen atoms, thus accounting for eight of the twelve valence electrons (four belonging originally to each carbon atom, and one to each hydrogen atom). The remaining four electrons are shared between the two carbon atoms. The carbon atoms are thus connected by *two* valence bonds and the structural formula,  $CH_2=CH_2$ , may be written. The presence of the *double bond* is characteristic of the olefins; it is the functional group of the series.

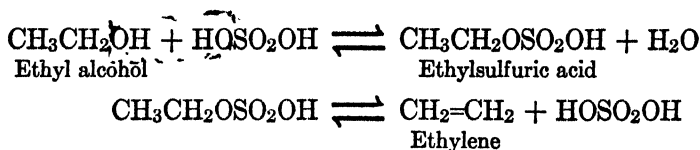
The names of the simple olefins are derived from those of the corresponding paraffins by changing the ending *ane* to *ylene*. The higher members are named according to the Geneva system, which uses the ending *ene*. In applying this system to compounds other than the paraffins, two modifications of the principles set forth on p. 11 are employed. These are as follows:

1. The substance is named as a derivative of the hydrocarbon corresponding to the longest chain *carrying the functional group*.
2. The location of the functional group is specified by numbering the carbon chain and incorporating into the name the number of the carbon atom to which the functional group is attached.

The use of these principles is illustrated in Table IV. For the lower members the common names are given in parentheses. It will be noted that only one number is used to locate the double bond. This is the *lower* of the two numbers corresponding to the carbon atoms connected by the double linkage.

Olefins are usually prepared in the laboratory by dehydration of alcohols. Ethylene, for example, may be obtained from ethyl alcohol by heating with concentrated sulfuric acid.





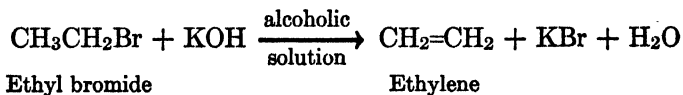
The second reaction occurs when the mixture is heated to about 150° and ethylene (gas) is generated. At lower temperatures ethylene and sulfuric acid combine in the reverse reaction. Since it is regenerated in the second reaction, sulfuric acid may be regarded as a catalyst for the

TABLE IV  
OLEFINS OR ETHYLENIC HYDROCARBONS

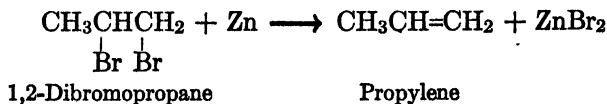
Name	Formula	Boiling Point
Ethene (ethylene)	$\text{CH}_2=\text{CH}_2$	-103.9°
Propene (propylene)	$\text{CH}_3\text{CH}=\text{CH}_2$	-47
1-Butene } (butylenes)	$\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$	-5
2-Butene }	$\text{CH}_3\text{CH}=\text{CHCH}_3$	2
Methylpropene (isobutylene)	$\text{CH}_3\text{C}=\text{CH}_2$	-6
1-Pentene	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	40
2-Pentene	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_3$	36.4
2-Methyl-2-butene	$\text{CH}_3\text{CH}=\text{CCH}_3$	38.4
3-Methyl-1-butene	$\text{CH}_3\text{CHCH}=\text{CH}_2$	25
2-Methyl-1-butene	$\text{CH}_2=\text{CCH}_2\text{CH}_3$	31

conversion of the alcohol to the olefin; other catalysts, such as aluminum oxide, phosphoric acid, or silica, may be used in its place.

Olefins also can be obtained by dehydrohalogenation of alkyl halides. This is usually accomplished by heating the alkyl halide with an alkali in the absence of water. Alcohol is often used as the solvent.

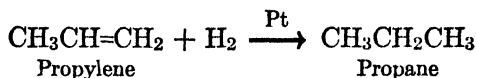


Olefins are sometimes prepared by the action of zinc on 1,2-dihalides.

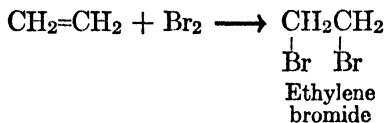


Large quantities of the lower olefins, particularly ethylene and propylene, are available as by-products of petroleum cracking (p. 12). They are among the cheapest organic compounds.

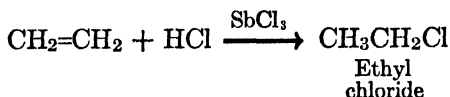
The characteristic chemical property of the olefins is their tendency to revert to saturated compounds. Thus, they combine with hydrogen in the presence of catalysts to give paraffins. Reactions of this type, involving the combination of two molecules to form a single product, are known as *addition* reactions.



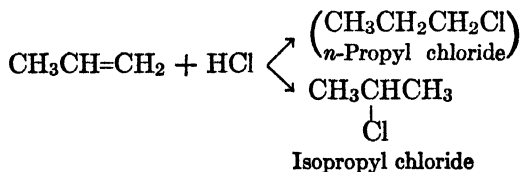
Olefins also undergo addition of chlorine and bromine at moderate temperatures and in the absence of catalysts. The products are again saturated compounds. Ethylene combines rapidly with bromine to give ethylene bromide.



Because this reaction causes the red color of bromine to disappear, it is often used as a laboratory test for unsaturation. Halogen acids react similarly, although less rapidly unless a catalyst is used. Ethyl chloride may be made by combining ethylene with hydrogen chloride in the presence of a catalyst such as antimony or bismuth trichloride.

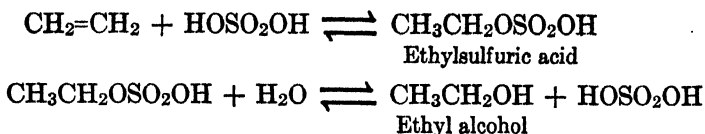


When an unsymmetrical reagent such as a hydrogen halide combines with an unsymmetrical olefin, two products might be expected. Propylene and hydrogen chloride, for example, might give either *n*-propyl chloride or isopropyl chloride, or both.

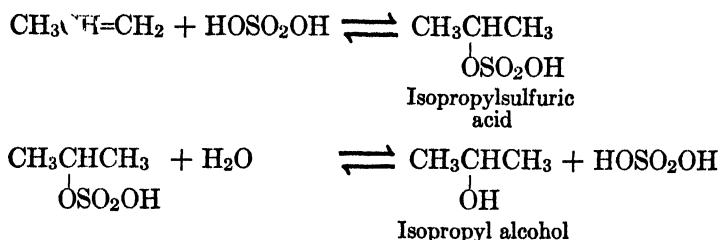


Actually, only isopropyl chloride is obtained. In such cases it is generally true that the *positive part of the reagent combines with the olefinic carbon atom which holds the larger number of hydrogen atoms*. This principle was first formulated by Markownikoff and is known as *Markownikoff's rule*.

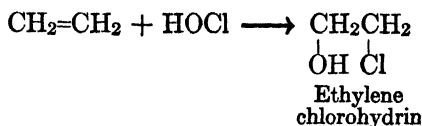
Olefins combine with sulfuric acid to form alkylsulfuric acids. The reaction is useful because the alkylsulfuric acids can be hydrolyzed to alcohols and sulfuric acid. By this method ethylene is converted to ethyl alcohol.



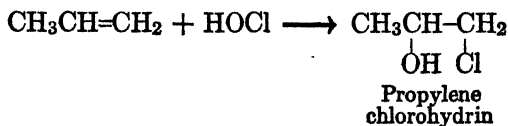
If propylene is employed the products are isopropylsulfuric acid and isopropyl alcohol.



Hypochlorous acid combines with olefins to produce compounds known as chlorohydrins. Ethylene yields ethylene chlorohydrin.



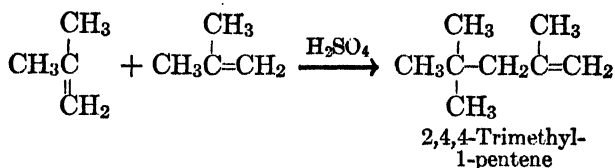
When hypochlorous acid reacts with unsymmetrical olefins the chlorine atom combines with the carbon which has the more hydrogen atoms. This is illustrated by the formation of propylene chlorohydrin from propylene.



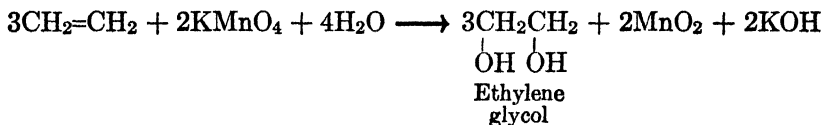
A recently discovered reaction of the olefins is their combination with branched-chain paraffins to give saturated hydrocarbons. For example, isobutane combines with propylene to form a heptane. The reaction is of value in the preparation of high-grade gasoline (p. 31).

Olefins may also be caused to combine with themselves, yielding unsaturated hydrocarbons of higher molecular weight. For example,

2,4,4-trimethyl-1-pentene ("isoöctene") is obtained by treatment of isobutylene with sulfuric acid.

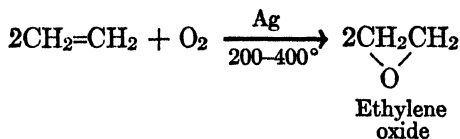


The ethylenic double bond is readily attacked by oxidizing agents, and this property is the basis of the Baeyer test for unsaturation. Potassium permanganate is used as the oxidizing agent because its reduction can be followed easily by the color change and, if the test is carried out in alkaline solution, by the formation of a precipitate of manganese dioxide.

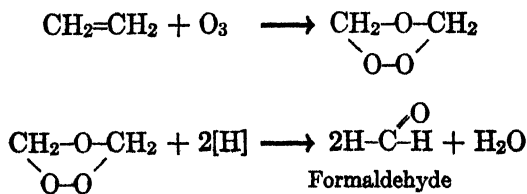


The reaction is not often useful for preparative purposes, since many of the glycols which might be made in this way are susceptible to oxidation by the permanganate.

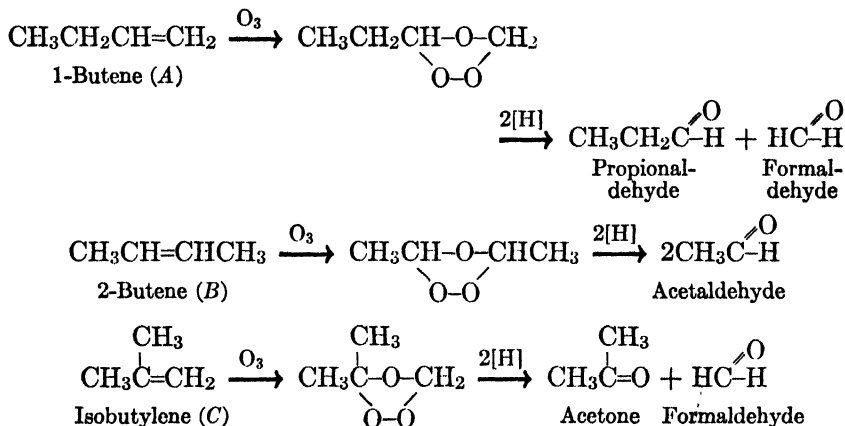
According to recent patents the oxidation of ethylene by atmospheric oxygen can be controlled so that ethylene oxide is produced. The reaction is carried out in the presence of a silver catalyst and at moderately high temperatures.



Ozone converts ethylenic hydrocarbons into ozonides, which are easily decomposed with cleavage of the carbon chain. For example, ethylene yields an ozonide which, upon hydrolysis in the presence of a reducing agent, is converted to formaldehyde.



This reaction is often used in the determination of structures of unsaturated substances. For example, of the three butylenes, one (*A*) on ozonization and reduction yields formaldehyde and propionaldehyde; the second (*B*) is converted to acetaldehyde and the third (*C*) yields acetone and formaldehyde. It follows, then, that *A* is 1-butene, *B* is 2-butene, and *C* is isobutylene.



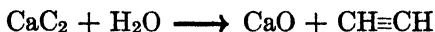
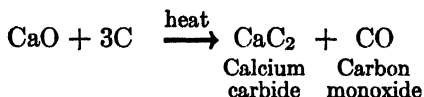
### The Acetylenes

Acetylene is the first member of a series of more highly unsaturated hydrocarbons; its formula is  $\text{C}_2\text{H}_2$  and, since it can be shown that each of the two carbon atoms carries one hydrogen atom, the structure must be  $\text{HC}\equiv\text{CH}$ . The series takes its name from the first member, and any compound containing the *triple bond* is said to be an acetylene. The systematic names of these hydrocarbons employ the ending *yne*; the simpler members, however, are usually named as substituted acetylenes. Examples of both systems of naming are given in Table V.

TABLE V  
ACETYLENES

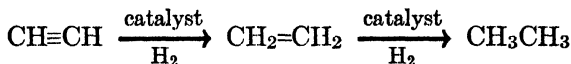
Name	Formula	Boiling Point
Acetylene (ethyne)	$\text{HC}\equiv\text{CH}$	$-88^\circ$
Methylacetylene (propyne)	$\text{CH}_3\text{C}\equiv\text{CH}$	$-24$
Ethylacetylene (1-butyne)	$\text{CH}_3\text{CH}_2\text{C}\equiv\text{CH}$	$18.5$
Dimethylacetylene (2-butyne)	$\text{CH}_3\text{C}\equiv\text{CCH}_3$	$29$
<i>n</i> -Propylacetylene (1-pentyne)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$	$40$

Acetylene is an important industrial raw material. It is obtained by heating coke with lime and decomposing the resulting calcium carbide with water. Carbon monoxide is formed along with calcium carbide.

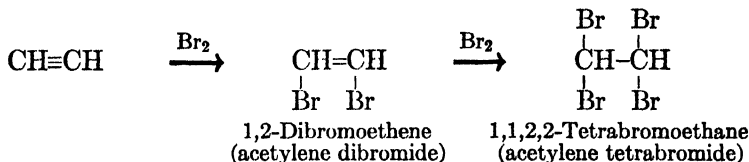


Acetylene is also obtained by cracking petroleum at high temperatures.

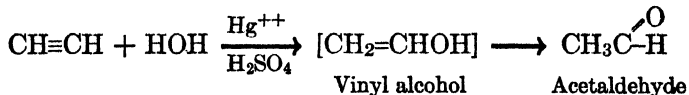
Acetylene and its homologs, like the olefins, are characterized by a marked tendency to combine with other reagents in such a way as to form saturated compounds. Their reactions usually differ from those of the olefins in that two moles of the adding reagent are required for saturation. The intermediate olefinic compound can often be obtained by limiting the amount of the reagent. Thus, either ethylene or ethane can be produced by hydrogenation of acetylene.



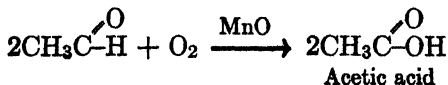
In a similar manner one or two molecules of halogen may combine with an acetylene. Thus, acetylene may be converted to the dibromide which in turn absorbs a molecule of bromine to yield the tetrabromide.



One of the important commercial uses of acetylene involves its reaction with water in the presence of sulfuric acid and mercury salts. Only one molecule of water is added. The addition product, vinyl alcohol, is unstable and rearranges to form acetaldehyde.

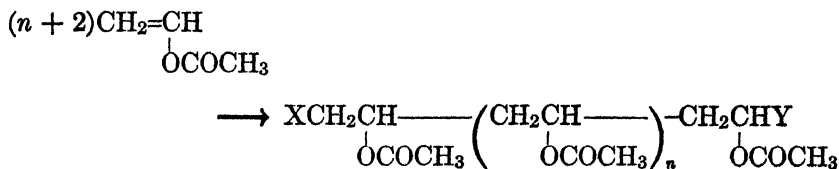


Nearly all simple compounds containing a hydroxyl group on a carbon atom which also carries an ethylenic double bond undergo the same rearrangement;  $\text{—C}=\text{C—OH} \longrightarrow \text{—CH—C}=\text{O}$ . Much of the acetaldehyde produced by hydration of acetylene is converted to acetic acid. In the process the aldehyde is oxidized by atmospheric oxygen in the presence of manganous oxide.





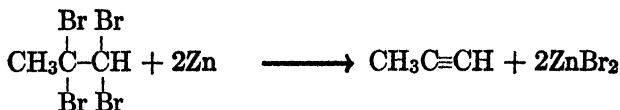
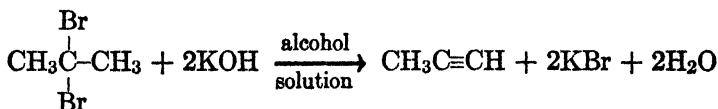
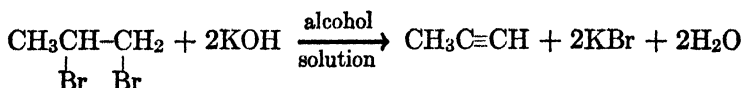
Vinyl acetate, like vinyl chloride, polymerizes readily; the product is known as polyvinyl acetate.



If vinyl acetate and vinyl chloride are mixed before polymerization, the polymer formed contains both units in the chain. Polymers of this type are known as *copolymers*. In this case the copolymer has properties which make it superior, for certain uses, to the polymer of either component. In general, the vinyl polymers are clear, transparent solids. They soften on heating, and so can be pressed into any desired shape in a hot mold; or the molten polymer can be drawn into filaments suitable for yarns. The new textile, Vinyon, is made in this way from a vinyl chloride-vinyl acetate copolymer.

The uses of ethylidene diacetate in the chemical industry are discussed in Chapter IX.

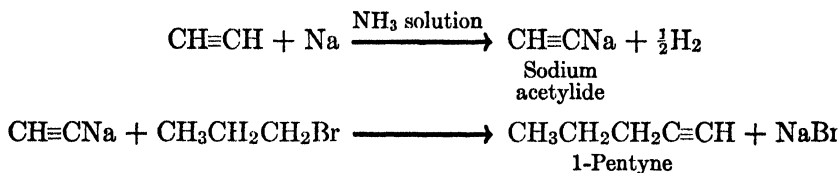
Acetylenes may be prepared by variations of the methods used for olefins. Dehydrohalogenation of a dihalide, or dehalogenation of a tetrahalide may be employed.



A very convenient synthesis of alkylacetylenes makes use of acetylene as the starting material. A hydrogen atom attached to an acetylenic carbon is weakly acidic and can be replaced by metals. Thus, acetylene and its homologs of the type  $\text{R}-\text{C}\equiv\text{CH}$  give insoluble silver salts ( $\text{R}-\text{C}\equiv\text{CAg}$ ) on treatment with ammoniacal silver solutions. In utilizing this property for synthesis, acetylene is treated with sodium in liquid ammonia solution. The resulting sodium acetylide is then treated



with an alkyl halide, yielding an acetylene of the type  $R-C\equiv CH$ . The preparation of 1-pentyne (*n*-propylacetylene) illustrates the synthesis.



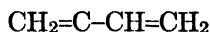
Since the monosubstituted acetylene ( $RC\equiv CH$ ) has one replaceable hydrogen atom, it might be supposed that it could be converted to the sodium derivative ( $RC\equiv CNa$ ) and this in turn to a disubstituted acetylene ( $RC\equiv CR'$ ) by treatment with an alkyl halide ( $R'X$ ). Sodium amide, rather than sodium, is used in preparing the salt  $RC\equiv CNa$ .

### The Diolefins

Many hydrocarbons with more than one point of unsaturation are known. Among the most important are those which contain two olefinic linkages; these are called diolefins or simply dienes. 1,3-Butadiene and isoprene are interesting examples.

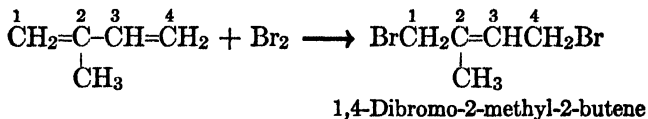


1,3-Butadiene



$$\begin{array}{c} CH_3 \\ | \\ \text{Isoprene} \end{array}$$

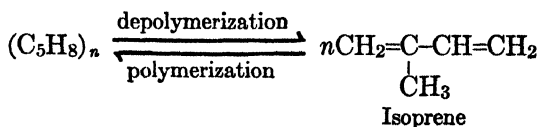
Each of these hydrocarbons has a system of *conjugated double bonds*, that is, a system of alternating double and single bonds. In such systems each double bond is strongly influenced by the other. A striking illustration is the reaction between bromine and isoprene.



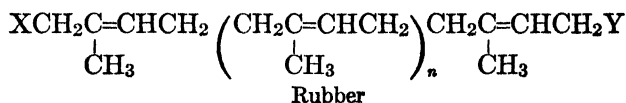
This is an example of the process known as 1,4-addition. It is generally true that addition takes place at the ends of a conjugated system. Apparently the double bonds partially neutralize each other when they are in this position and the property of unsaturation develops only at points, such as the ends of the system, where the conjugation is interrupted.

Isoprene is obtained when rubber is heated in the absence of air. In the presence of sodium the isoprene changes to a material which

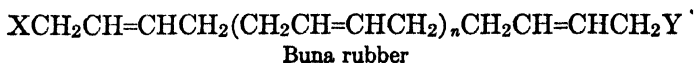
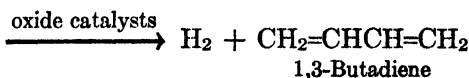
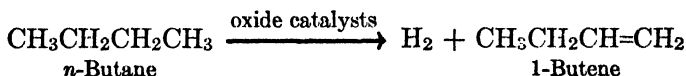
closely resembles natural rubber. Since analysis of rubber shows it to have the formula  $(C_5H_8)_n$ , it is apparent that rubber is a polymer of isoprene.



Evidence indicates that the isoprene units in rubber are combined by a process similar to 1,4-addition, and that the polymeric molecule contains about 1,000 isoprene units.

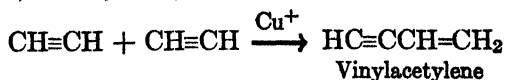


In recent years chemists have been successful in the synthesis of rubber-like materials. The best-known synthetic rubbers are those of the Buna type. Buna rubber is made by polymerization of 1,3-butadiene. The diene can be obtained by dehydrogenation of *n*-butane, which is available in large quantities from petroleum.



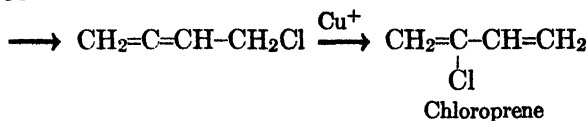
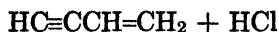
The best types of Buna rubber are *copolymers*, that is, another substance capable of polymerization is added to the butadiene and the resulting polymer contains both units in the chain (p. 363).

Neoprene is a synthetic rubber which is manufactured from acetylene. The first operation is the *dimerization* of acetylene, in the presence of cuprous salts, to vinylacetylene.

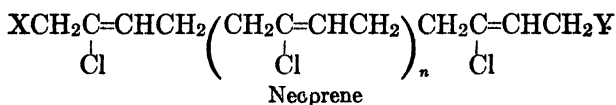


Vinylacetylene combines with hydrogen chloride but, although the

expected 1,4-addition occurs, the product rearranges in the presence of copper salts to give chloroprene.



If the reaction is carried out in the presence of copper salts chloroprene is obtained directly. Chloroprene differs from isoprene in having a chlorine atom in place of the methyl group, and like isoprene it polymerizes readily. The polymer is known as Neoprene.



Neoprene has many of the physical properties of rubber. Unlike rubber, it retains its tensile strength and elasticity when it is in contact with organic liquids. Consequently it finds uses in gasoline and oil lines, for which rubber is not suited.

### PROBLEMS

- ✓ 1. Write equations for the reaction of 1-butene with: hydrogen (platinum catalyst); bromine (at room temperature and in the absence of strong light); sulfuric acid, followed by hydrolysis; hydrogen chloride; ozone, followed by treatment with zinc and water; aqueous, alkaline potassium permanganate; hypochlorous acid.
2. Define and illustrate the following terms: functional group; addition reaction; conjugated system; 1,4-addition; polymerization; copolymer.
3. Write the formulas of *n*-butane, cyclobutane, 1-butene, 1-butyne, 1,3-butadiene. Compare their reactions with bromine, with respect to type of reaction, conditions required, and number of products obtained.
4. What are the commercial sources of ethylene? acetylene? 1,3-butadiene?
5. By means of a formula, show the probable structure of rubber. Give equations for the preparation of Neoprene from acetylene; of Buna rubber from petroleum.
6. Give equations for a synthesis of 1-butyne from ethylene, acetylene, and any required inorganic reagents.

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## CHAPTER V

### PETROLEUM

The principal constituents of petroleum are saturated hydrocarbons. Both paraffins and cycloparaffins may be present; cycloparaffins occurring in petroleum are often called naphthenes. Crude oils are usually classified as paraffin-base oils or asphalt-base oils. The distinction is made on the basis of the residue, paraffin or asphalt, which remains when the oil is distilled. In addition to hydrocarbons, crude petroleum contains smaller amounts of organic nitrogen and sulfur compounds.

Because it contains many related hydrocarbons, petroleum is difficult to separate into its individual components. By controlled distillation it can be separated into fractions of decreasing volatility. These fractions, each of which contains a large number of hydrocarbons, are used as fuels and lubricants. An idea of the composition of the common petroleum products may be gained from Table VI.

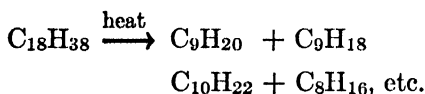
TABLE VI  
FRACTIONAL DISTILLATION OF PETROLEUM

Boiling Point	Composition	Name
Gaseous	$\text{CH}_4\text{--C}_4\text{H}_{10}$	Natural gas
20–100°	$\text{C}_5\text{H}_{12}\text{--C}_7\text{H}_{16}$	Naphtha, ligroin, petroleum ether
70–200	$\text{C}_6\text{H}_{14}\text{--C}_{12}\text{H}_{26}$	Gasoline
200–275	$\text{C}_{12}\text{H}_{26}\text{--C}_{15}\text{H}_{32}$	Kerosene
Above 275	$\text{C}_{15}\text{H}_{32}\text{--C}_{18}\text{H}_{38}$	Gas oil (cracking stock)
	$\text{C}_{16}\text{H}_{34}\text{--C}_{20}\text{H}_{42}$	Lubricating oil, mineral oil
	$\text{C}_{18}\text{H}_{38}\text{--C}_{22}\text{H}_{46}$	Greases, vaseline
	$\text{C}_{20}\text{H}_{42}\text{--C}_{24}\text{H}_{50}$	Paraffin wax
Residue		Asphalt tar, petroleum coke

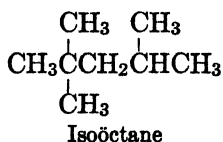
The fractional distillation of an average crude oil yields a relatively small gasoline fraction, with larger amounts of kerosene and gas oil. Consequently chemists have long sought methods of converting these higher-boiling materials into gasoline. This is now accomplished in the cracking process, by which the large paraffins are decomposed at high temperatures to give a mixture of smaller paraffins and olefins (p. 9). The operation is carried out in cracking stills which permit the escape of

the newly formed volatile hydrocarbons from the cracking zone. A portion of the cracking distillate is too volatile for use as gasoline, since cleavage near the end of the carbon chains produces hydrocarbons of low molecular weight (p. 12). Nevertheless, the process is of tremendous economic value, since it enables refiners to convert as much as 80 per cent of the crude oil into gasoline whereas only about 20 per cent could be obtained by fractional distillation.

The cracking process not only has increased the quantity of gasoline available, but also has improved its quality. Gasoline made in this way has less tendency to cause knocking in a high-compression engine than the straight-run gasoline obtained by direct distillation of petroleum. The unsaturated hydrocarbons in the cracked gasoline are responsible for the improved anti-knock property.



The anti-knock value of a gasoline is usually expressed in terms of the octane number. This term came to be used in the early studies of knocking because, of a great variety of *pure* hydrocarbons tested, iso-octane (2,2,4-trimethylpentane) was found to have the least tendency to knock. *n*-Heptane was found to have the poorest characteristics, so far as knocking is concerned.



*n*-Heptane

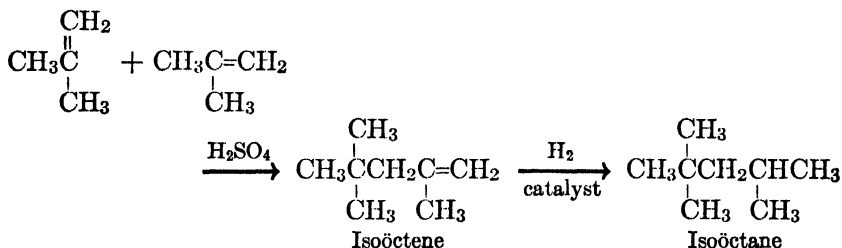
These two hydrocarbons were selected as reference points for the evaluation of gasolines. A fuel of 80 octane rating is one which has the same tendency to knock as a mixture of 80 parts of iso-octane and 20 parts of *n*-heptane. It should be emphasized that the octane number does not refer to the composition of a gasoline, but only to its knocking characteristics.

The improvements in the anti-knock qualities of gasoline have had far-reaching effects on the design of internal-combustion engines. An engine of given size can be made to operate more efficiently by increasing its compression ratio. However, when the compression ratio is increased it becomes necessary to employ a fuel of higher octane rating to avoid knocking. Consequently, as the octane value of commercial gasoline is increased, automobile engines become smaller, more powerful,

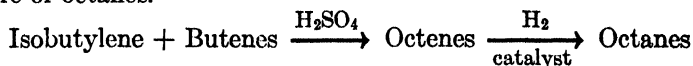
and more efficient. These factors are of even greater importance in connection with airplane engines, since an improved fuel not only results in a more powerful machine but also extends the cruising range without increasing the fuel load.

As indicated above (p. 12), the cracking process converts a part of the heavier paraffins into gaseous hydrocarbons. Both saturated and unsaturated hydrocarbons are produced. These are methane, ethane, ethylene, propane, propylene, *n*-butane, 1-butene, 2-butene, isobutane, and isobutylene, together with pentanes and pentenes. Since the unsaturated hydrocarbons are reactive they are of value as raw materials, and large quantities of ethylene, propylene, butenes, and isobutylene are utilized by the chemical industry.

In recent years methods of recombining the small hydrocarbon molecules have been discovered. These processes yield hydrocarbons of the gasoline range and the products have very high octane ratings. The method first employed consists in treating isobutylene with sulfuric acid to produce isoöctene. Hydrogenation of the latter converts it to isoöctane (p. 30).



If a mixture of isobutylene and the butenes (1-butene and 2-butene) is employed, the isobutylene reacts preferentially with the butenes. The product is a mixture of octenes which can be hydrogenated to a mixture of octanes.



More recently it has been found that branched-chain paraffins combine with olefins under the influence of acid catalysts (p. 20). The reaction between isobutane and the butylenes produces octanes directly.



The paraffins produced in condensations of this type are not those which would be expected if the reaction were a simple addition of the iso-



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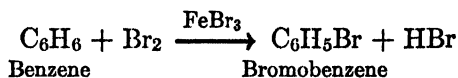


## CHAPTER VI

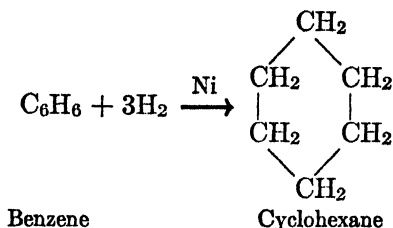
### AROMATIC HYDROCARBONS

A number of hydrocarbons have been isolated from coal tar, the black viscous material which distills when coke is prepared by heating coal at 1100–1300°. These are sometimes called the coal tar hydrocarbons, but they are more generally referred to as the aromatic hydrocarbons. The simplest member of this family is benzene,  $C_6H_6$ .

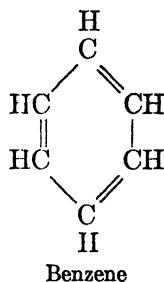
Comparison of the formula of benzene with that of a paraffin of six carbon atoms indicates that the hydrocarbon is highly unsaturated. Yet it is almost devoid of the properties which distinguish the olefins and acetylenes. For example, it does not respond to the Baeyer test (p. 21), and when it is treated with a halogen in the absence of a catalyst no reaction occurs. If a catalyst such as an iron or aluminum halide is present, a reaction does occur, but it is one of substitution rather than of addition. Thus, so far as the type of reaction with halogens is concerned, benzene resembles the paraffins rather than the olefins. On the other hand, the halogenation of benzene differs from that of a hexane in requiring a different catalyst and in producing a single product rather than a mixture of isomers. For example, an excellent yield of bromobenzene is obtained by treating benzene with bromine in the presence of iron. Presumably the iron is converted to ferric bromide which is the catalyst.



The fact that a single bromobenzene is formed, although it might be expected that the bromine could become attached to any one of the six carbon atoms, suggests that benzene is a cyclic compound in which all the carbon atoms are equivalent. That a ring is present is proved by the catalytic hydrogenation of benzene. Under conditions similar to those employed in hydrogenating olefins or acetylenes, benzene is unaffected, but at higher temperatures and pressures it is converted to cyclohexane.

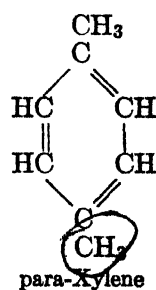
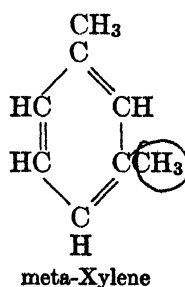
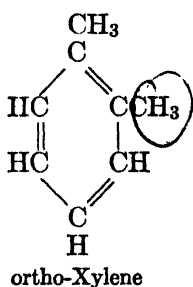
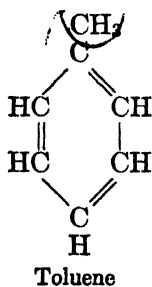


This indicates that the formula of benzene differs from that of cyclohexane by the presence of three double bonds. Such a formula was proposed by Kekulé in 1865.

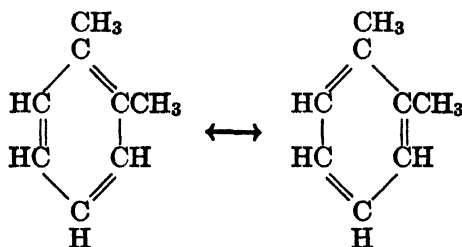


Although benzene does contain double linkages, it is not to be compared to the olefins. It will be recalled that in the conjugated dienes the double bonds tend to neutralize each other except at the ends of the system, and consequently tend to undergo 1,4 addition. Benzene is to be regarded as having a *completely* conjugated system, so that the mutual neutralization of the double bonds is at a maximum.

A number of homologs of benzene are found along with it in the light fraction from the distillation of coal tar. Among them are toluene and the xylenes. The xylenes, or dimethylbenzenes, illustrate a type of isomerism which is very common in the aromatic series. The two methyl groups may be placed in three different positions with respect to each other; these isomers differ in *orientation*.

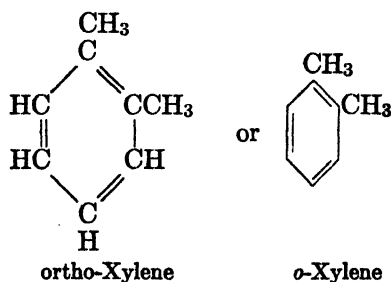


One of the early objections to Kekulé's formula for benzene was based on the argument that it indicates the existence of two forms of *ortho*-xylene, depending on the position of the double bonds.

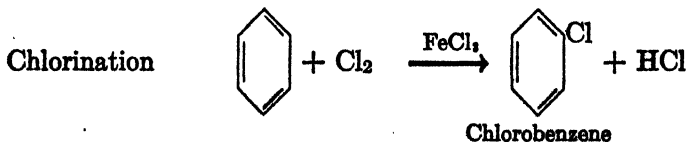


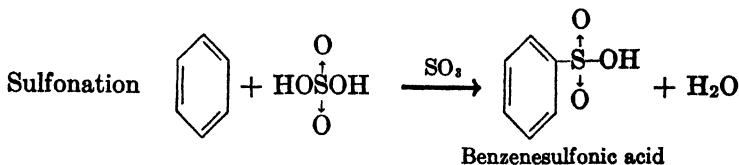
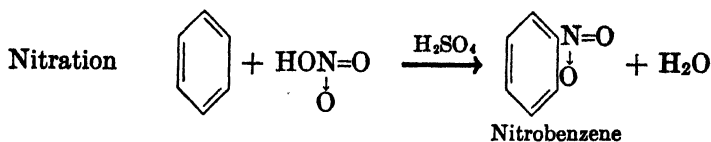
It has been found, by examination of the products of ozonization (p. 21), that both forms are present in ordinary *ortho*-xylene. Since no one has ever been able to separate them it is assumed that the two forms are in equilibrium with each other. In other words, the double bonds of the benzene ring are not fixed but oscillate between the two possible positions.

For convenience in writing formulas the benzene ring is ordinarily represented by a hexagon with alternate double and single bonds. In naming aromatic substances the prefixes *ortho*, *meta*, and *para* are abbreviated, only the first letters being used. These abbreviations are illustrated in the formulas below.



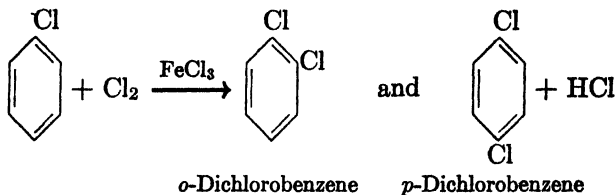
The aromatic hydrocarbons react with the halogens, with nitric acid, and with sulfuric acid to give products of substitution. The reactions can be made to give good yields of mono-substituted products by limiting the amounts of the reagents.



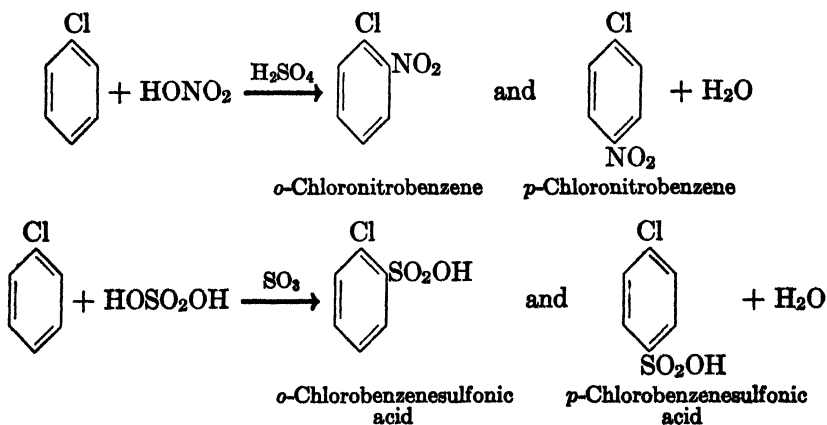


These reactions occur at moderate temperatures when the catalysts indicated are present.

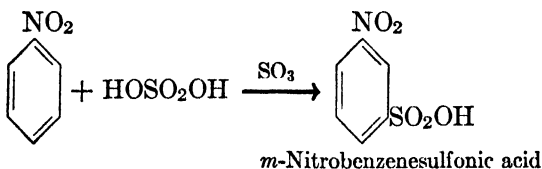
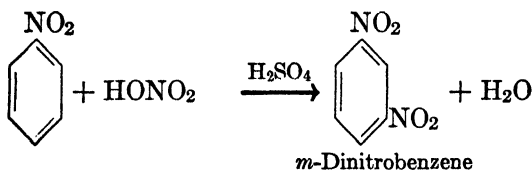
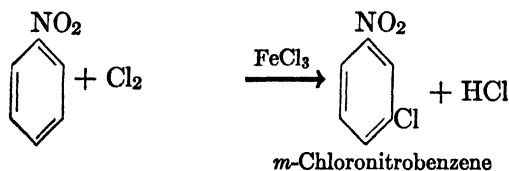
By using appropriate amounts of reagents disubstituted products can be obtained. With two molecules of chlorine, benzene yields a mixture of *o*- and *p*-dichlorobenzenes. The same products are obtained from chlorobenzene and one molecule of chlorine.



In other substitutions chlorobenzene likewise yields *both ortho and para* isomers.



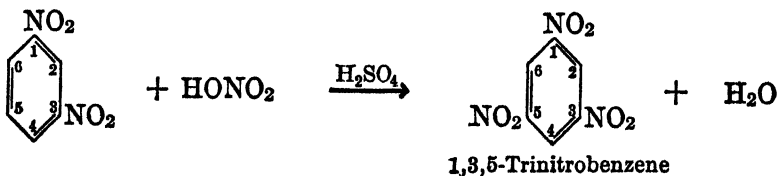
On the other hand, substitutions carried out on nitrobenzene yield the *meta* isomer.



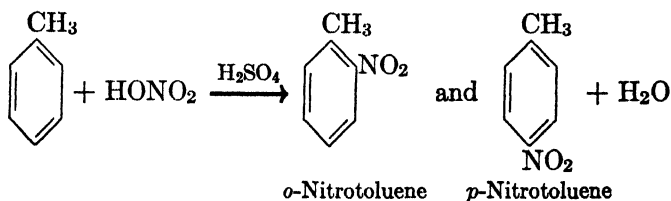
These examples illustrate a general truth: the position taken by the second substituent entering a benzene ring is determined by the nature of the substituent already present. Certain groups, like  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CH}_3$ , and  $-\text{CH}_2\text{CH}_3$ , are *ortho*, *para*-directing, that is, when they are attached to the benzene ring they cause the second substituent, regardless of its nature, to enter the *ortho* and *para* positions. The common *meta*-directing groups are  $-\text{NO}_2$ ,  $-\text{SO}_2\text{OH}$ , and  $-\text{CO}_2\text{H}$ .

A rule which is very useful in predicting the directive influence of a group attached to the benzene ring has been formulated by Hammick and Illingworth. The rule states that if, in the compound  $\text{C}_6\text{H}_4\text{XY}$ , Y is to the right of X in the periodic table or above X, if X and Y are in the same group, then  $-\text{XY}$  is *meta*-directing. In all other cases, including that in which  $-\text{XY}$  is a single atom,  $-\text{XY}$  is *ortho*, *para*-directing. There are few exceptions to this rule.

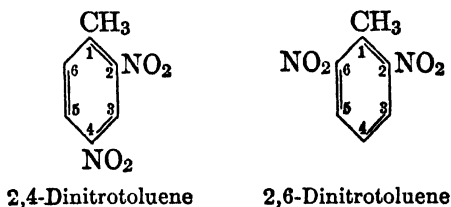
When a third group is introduced into the ring the directive influences of both the first two must be considered. Sometimes the directive influences reinforce each other, as in *m*-dinitrobenzene. Introduction of a third nitro group gives only the symmetrical trinitrobenzene, since each nitro group directs the entering group to the 5 position.



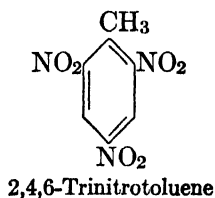
A similar situation is encountered in the nitration of toluene. The first products are, of course, *o*- and *p*-nitrotoluene.



In *o*-nitrotoluene both the methyl group and the nitro group will direct a third group to the 4 and 6 positions. In the *para* isomer the 2 and 6 positions are activated. If a second nitro group is introduced by nitration of the mixture of *o*- and *p*-nitrotoluenes two isomeric dinitrotoluenes may be produced.



In the first of these isomers further substitution will take place in the 6 position, and in the second isomer in the 4 position. Further nitration of the mixture therefore gives a single product, 2,4,6-trinitrotoluene (TNT).

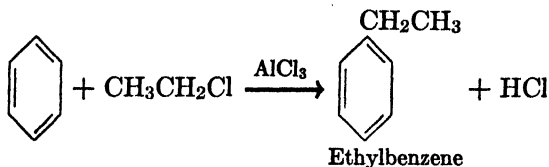


When the directive influences oppose each other a variety of further substitution products may be formed. In *m*-chloronitrobenzene, for example, the entering group will be directed to the 5 position by the nitro-group and to the 2, 4, and 6 positions by the chlorine atom.

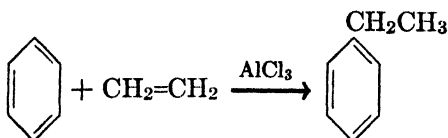


A type of reaction somewhat different from the substitutions discussed above is the Friedel-Crafts reaction. It takes place when alu-

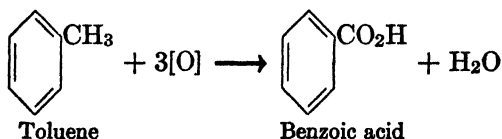
minum chloride is added to a mixture of an aromatic hydrocarbon and an alkyl halide. For example, ethyl chloride and benzene yield ethylbenzene.



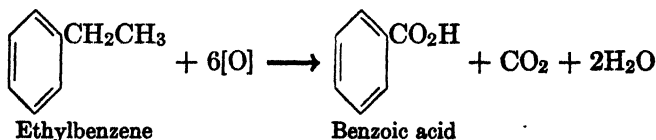
If ethylene is used in place of the halide the same product is formed by an addition reaction.



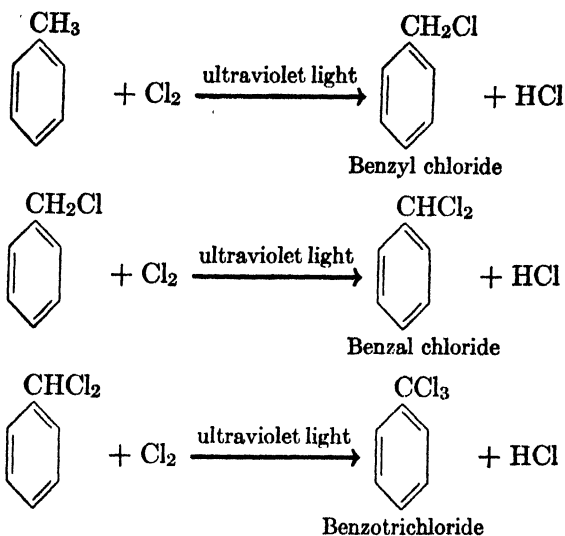
Certain substances, like toluene, ethylbenzene, and the xylenes, can be considered as mixed hydrocarbons, since they contain both aromatic and paraffinic portions. The properties of such compounds are of interest in affording comparisons of aromatic and paraffinic hydrocarbons. For instance, when toluene is subjected to vigorous oxidation, it is the methyl group rather than the benzene ring which is affected. The product is benzoic acid, the simplest aromatic acid.



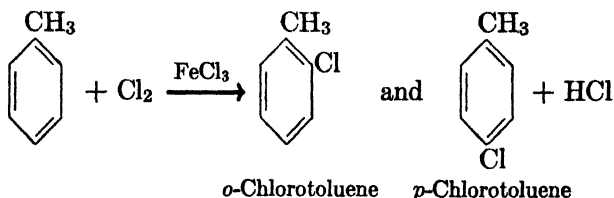
If a longer paraffin side chain is present all its carbon atoms except the attached to the ring are converted to carbon dioxide.



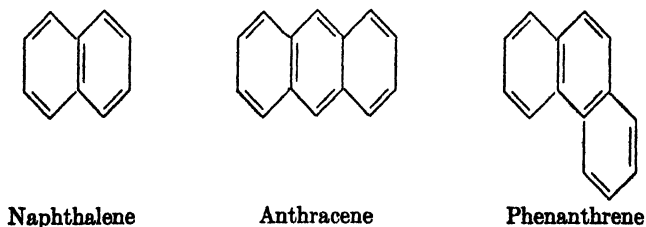
The halogenation of toluene affords an illustration of the specificity of catalysts. If toluene is chlorinated in the presence of strong light, substitution in the methyl group occurs. Either one, two, or three hydrogens can be replaced by regulating the amount of chlorine used.



If chlorination is carried out in the presence of ferric chloride, substitution in the aromatic nucleus occurs, yielding a mixture of *o*- and *p*-chlorotoluenes.



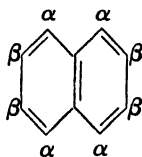
A second type of aromatic hydrocarbon found in coal tar is that containing more than one benzene ring. Examples are naphthalene ( $\text{C}_{10}\text{H}_8$ ), anthracene ( $\text{C}_{14}\text{H}_{10}$ ), and phenanthrene ( $\text{C}_{14}\text{H}_{10}$ ).



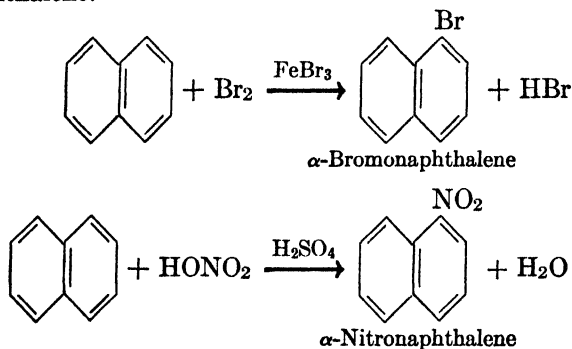
From the commercial standpoint the most important of these is naphthalene. It is the most abundant of the hydrocarbons isolated from coal tar and has found many uses in the preparation of dyes, medicinals, and other substances.



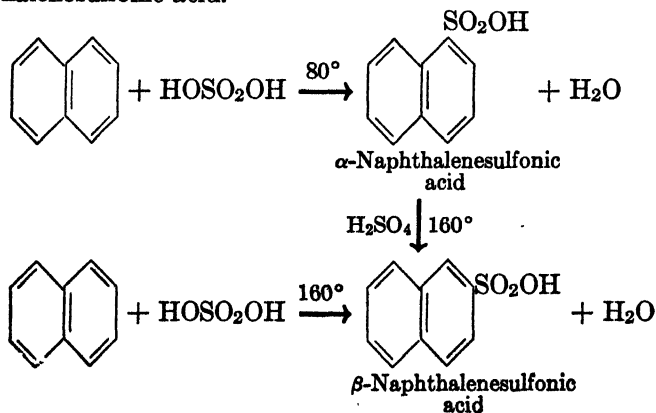
Examination of the formula of naphthalene reveals that there are two possible monosubstitution products. The positions designated by  $\alpha$  in the formula below are equivalent, as are also those designated by  $\beta$ .



Generally, naphthalene yields the  $\alpha$ -derivative in substitutions. For example, bromination gives  $\alpha$ -bromonaphthalene, and nitration yields  $\alpha$ -nitronaphthalene.

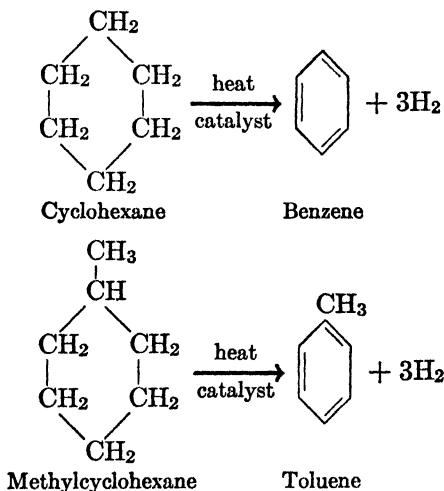


Sulfonation, on the other hand, may produce either the *alpha* or *beta* derivative, depending on the temperature of the reaction mixture. At low temperatures ( $80^\circ$ )  $\alpha$ -naphthalenesulfonic acid is produced. If this product is heated to about  $160^\circ$  in the presence of sulfuric acid it rearranges to the *beta* isomer. Consequently sulfonation at  $160^\circ$  produces  $\beta$ -naphthalenesulfonic acid.

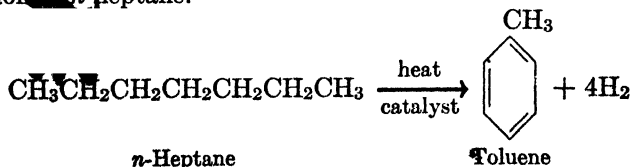


**Preparation of Aromatic Hydrocarbons from Petroleum.** Most of the coke produced today is used in the steel industry. Coal tar and the aromatic hydrocarbons may therefore be regarded as by-products of steel manufacturing. In normal times the amounts so produced are sufficient for the needs of the chemical industry. In fact, the blending of benzene with gasoline and the use of toluene as a diluent for lacquer solvents indicate that both these hydrocarbons have been available in abundance. In time of war, however, the demand for trinitrotoluene (p. 39) may far exceed the supply of toluene. For this reason chemists have sought other sources of aromatic hydrocarbons.

Crude oil which contains a high percentage of naphthenes (cycloparaffins) affords a source of aromatic hydrocarbons. Benzene may be prepared from cyclohexane and toluene from methylcyclohexane.



More striking is the conversion of straight-chain paraffins to aromatics. Toluene is obtained in good yields by dehydrogenation and cyclization of *n*-heptane.

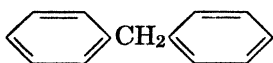


This process is now employed to produce toluene from the heptane fraction of petroleum.

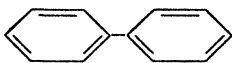
### Classification of Organic Compounds

The three major classes of organic compounds are the aliphatic, the alicyclic, and the aromatic substances. Aliphatic compounds include all derivatives of the open-chain hydrocarbons, such as the paraffins, olefins, and acetylenes. The closely related alicyclic compounds are derivatives of the cycloparaffins. Aromatic compounds are those which contain one or more rings of the benzene type.

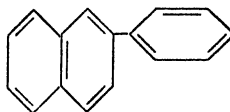
The groups derived from aromatic hydrocarbons by removal of one hydrogen atom are called aryl groups. Chlorobenzene and bromonaphthalene are termed aryl halides. The group so derived from benzene is known as the phenyl group. This term arose from an early attempt to use the name phen instead of benzene. Curiously enough, the name was accepted as the stem for naming derivatives but is no longer used for the hydrocarbon. Examples of its use are indicated below.



Diphenylmethane



Biphenyl

 $\beta$ -Phenylnaphthalene

### PROBLEMS

1. With respect to the type of reaction and the conditions required, compare the reactions of cyclohexane, cyclohexene, and benzene with bromine.
2. By application of the Hammett-Ingold rule, predict the directive influence of the trichloromethyl group in benzotrichloride.
3. Give equations for useful methods of synthesis of the following: *p*-dibromobenzene, *m*-nitrobromobenzene, *p*-nitrobromobenzene, *p*-nitrobenzotrichloride,  $\alpha$ -chloronaphthalene.
4. What is the maximum number of monosubstitution products which may be obtained by the action of bromine in the presence of iron on *o*-xylene? *m*-xylene? *p*-xylene?
5. Give equations for the reactions involved in the preparation of TNT from petroleum.

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ASHDOWN, "Earliest History of the Friedel-Crafts Reaction," *Ind. Eng. Chem.*, **19**, 1063 (1927).  
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## CHAPTER VII

### ALCOHOLS

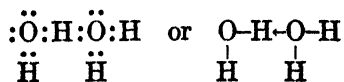
Those compounds which contain a hydroxyl group attached to an aliphatic or alicyclic hydrocarbon residue are known as alcohols. The simple alcohols thus have the formula  $C_nH_{2n+1}OH$ . Their functional group is the hydroxyl group. Their chemical properties are those of the hydroxyl group and those of the paraffin group  $C_nH_{2n+1}$ . It will be seen that the properties of the hydrocarbon residue are modified by the presence of the hydroxyl group. The following are some of the simpler alcohols; in the systematic names the suffix *ol* indicates the hydroxyl group.

TABLE VII

#### STRAIGHT-CHAIN PRIMARY ALCOHOLS

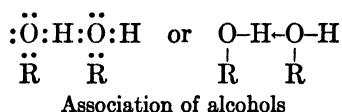
Name	Structural Formula	Boiling Point
Methyl alcohol (methanol)	$CH_3OH$	65°
Ethyl alcohol (ethanol)	$CH_3CH_2OH$	78
<i>n</i> -Propyl alcohol (1-propanol)	$CH_3CH_2CH_2OH$	97
<i>n</i> -Butyl alcohol (1-butanol)	$CH_3CH_2CH_2CH_2OH$	117
<i>n</i> -Amyl alcohol (1-pentanol)	$CH_3CH_2CH_2CH_2CH_2OH$	137
<i>n</i> -Hexyl alcohol (1-hexanol)	$CH_3CH_2CH_2CH_2CH_2CH_2OH$	157

It is interesting to note that these compounds have boiling points much higher than those of the corresponding paraffins. Compounds having hydroxyl groups usually are less volatile than other substances of similar molecular weight. Indeed, water (b.p. 100°) boils much higher than the hydrides of other elements near oxygen in the periodic table ( $NH_3$ , b.p. -78°;  $H_2S$ , b.p. -62°;  $HCl$ , b.p. -84°). It has been found that the abnormal boiling point of water is due to the association of water molecules. This association involves the formation of a coordination bond between the hydrogen atom of one molecule of water and the oxygen atom of another. In the process the hydrogen atom acquires a shell of four electrons.



Association of water

The boiling points of the alcohols indicate that a similar association occurs even though one of the hydrogen atoms of water has been replaced by an alkyl group.



The coordination bond formed between a hydrogen atom and a donor atom, such as exists in water and the alcohols is often called the "hydrogen bond"; a better although less generally used term is "hydrogen bridge."

### Isomerism and Classification of Alcohols

In the examples given in the preceding table the hydroxyl group is situated at the end of the carbon chain. These alcohols, represented by the formula  $\text{RCH}_2\text{OH}$  are *primary* alcohols. The isomeric propyl alcohol has the formula  $\text{CH}_3\text{CHCH}_3$  and is known as isopropyl alcohol



(2-propanol). Alcohols such as this, represented by  $\text{R}_2\text{CHOH}$ , are *secondary* alcohols. There are four butyl alcohols, including two which

TABLE VIII  
THE ISOMERIC BUTYL ALCOHOLS

Name	Class	Formula	Boiling Point	Solubility in Water at 20° g. per 100 g. H <sub>2</sub> O
<i>n</i> -Butyl alcohol (1-butanol)	Primary	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	118°	7.9
Isobutyl alcohol (2-methyl-1-propanol)	Primary	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{CHCH}_2\text{OH} \end{array}$	108	9.5
<i>sec</i> -Butyl alcohol (2-butanol)	Secondary	$\begin{array}{c} \text{OH} \\   \\ \text{CH}_3\text{CH}_2\text{CHCH}_3 \end{array}$	100	12.5
<i>t</i> -Butyl alcohol (2-methyl-2-propanol)	Tertiary	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{COH} \\   \\ \text{CH}_3 \end{array}$	83	∞

are primary, one which is secondary and one, represented by the formula  $\text{R}_3\text{COH}$ , which is *tertiary*. Their formulas and names are given in Table VIII. The boiling points and solubilities in water of these alcohols provide an excellent example of the wide variations which may exist in the properties of isomeric substances.

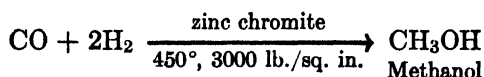
There are eight amyl alcohols. Three are derived from *n*-pentane, four from isopentane, and one from neopentane (see p. 11). Their names, formulas, and classes are given in Table IX. A system of naming alcohols as carbinols is illustrated in this table. In this system methyl alcohol ( $\text{CH}_3\text{OH}$ ) is given the name *carbinol*, and higher alcohols are named as substituted carbinols; e.g., ethyl alcohol is methylcarbinol, isopropyl alcohol is dimethylcarbinol, and *t*-butyl alcohol is trimethylcarbinol.

TABLE IX  
THE AMYL ALCOHOLS

Name		Class	Formula
Geneva system	Carbinol system		
1-Pentanol	<i>n</i> -Butylcarbinol	Primary	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$
2-Pentanol	Methyl- <i>n</i> -propylcarbinol	Secondary	$\text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{OH}}{\text{CH}}\text{CH}_3$
3-Pentanol	Diethylcarbinol	Secondary	$\text{CH}_3\text{CH}_2\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}_3$
3-Methyl-1-butanol	Isobutylcarbinol	Primary	$\text{CH}_3\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\text{OH}$
3-Methyl-2-butanol	Methylisopropylcarbinol	Secondary	$\text{CH}_3\underset{\text{CH}_3}{\text{CH}}\underset{\text{OH}}{\text{CH}}\text{CH}_3$
2-Methyl-2-butanol	Dimethylethylcarbinol	Tertiary	$\text{CH}_3\underset{\text{CH}_3}{\text{C}}\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CH}_3$
2-Methyl-1-butanol	<i>sec</i> -Butylcarbinol	Primary	$\text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{OH}$
2,2-Dimethyl-1-propanol	<i>t</i> -Butylcarbinol	Primary	$\text{CH}_3\underset{\text{CH}_3}{\text{C}}\underset{\text{CH}_3}{\text{CH}}_2\text{OH}$

**Preparation of Alcohols.** A number of general methods of preparing alcohols from other organic compounds, such as aldehydes, ketones, and esters, are discussed in later chapters. In this section are given some of the commercial methods of preparing the lower alcohols.

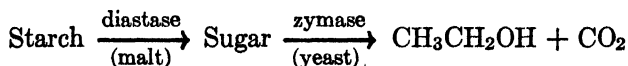
*Methyl alcohol.* Most of the methyl alcohol produced today is prepared from carbon monoxide and hydrogen. The raw materials are coke and water. Water gas is first prepared, then mixed with hydrogen and passed over a zinc chromite catalyst at a pressure of about 3000 lb per square inch and at a temperature of 450°.



The methyl alcohol produced in this way is of very high purity (99.9%).

Methyl alcohol has been called wood alcohol because it is a by-product of the wood charcoal industry. Water, acetone, and acetic acid are formed along with methyl alcohol, so that it is difficult to obtain the alcohol in a pure state from this source. The method is of little importance at the present time.

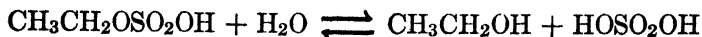
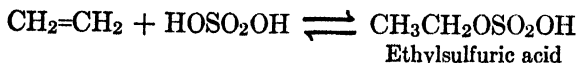
*Ethyl alcohol* is prepared from sugar by fermentation. When pure alcohol for industrial purposes is desired the raw material is molasses. In the preparation of alcoholic beverages from grains, the starch of the grain must first be converted to sugar. This is accomplished by treating the grain with malt. Malt is prepared by heating sprouted barley to a temperature sufficiently high to kill the barley but not to destroy a substance, known as diastase, which catalyzes the transformation of starch into sugar. Diastase is an example of a group of substances known as enzymes, compounds synthesized by living organisms for the purpose of catalyzing certain organic reactions. The transformation of sugar into alcohol is brought about by the enzyme zymase which is present in yeast.



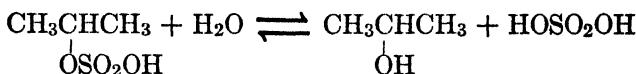
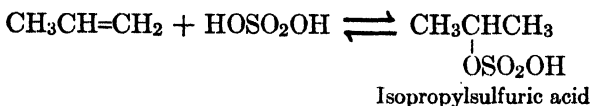
The fermentation is carried out in water solution and yields a dilute solution (14 to 18 per cent) of ethyl alcohol, along with small amounts of amyl alcohols. By fractional distillation the constant-boiling mixture of 95.5 per cent alcohol and 4.5 per cent water is obtained. This is the ordinary ethyl alcohol of commerce. If anhydrous ("absolute") alcohol is desired the water is removed chemically or by redistillation in the presence of benzene. The latter method depends on the fact that benzene, water, and alcohol form a constant-boiling mixture of boiling point 65°. Benzene and alcohol form another constant-boiling mixture of boiling point 68°. Thus, if benzene is added to ordinary alcohol and the mixture is fractionated, the first fraction, consisting of benzene, water, and alcohol, is collected at 65°. If benzene is present in excess, this will be followed by a fraction at 68°, consisting of benzene and alcohol. The last fraction, distilling at 78.3°, is anhydrous ethyl alcohol.

The conversion of ethylene (from cracking stills) to ethanol already has been mentioned (p. 20). The ethylene is dissolved in concentrated

sulfuric acid, yielding ethylsulfuric acid. Water is then added to hydrolyze the ethylsulfuric acid to ethyl alcohol and sulfuric acid.

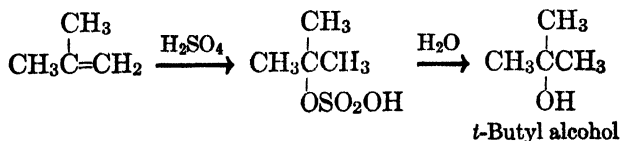
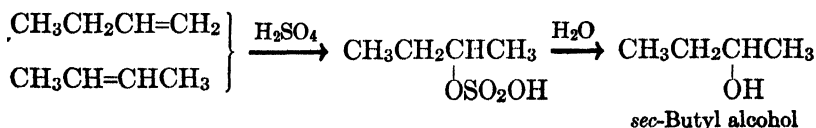


*Isopropyl alcohol* is prepared from propylene by the same method (p. 20). It is to be noted that ethylene is the only olefin which leads to a primary alcohol (Markownikoff's rule, p. 19).



*n*-Propyl alcohol and *isobutyl alcohol* are obtained by the condensation under high-pressure of carbon monoxide with hydrogen in the presence of zinc chromite and an alkali. The products with the alkaline catalyst are methanol, ethanol, *n*-propyl alcohol, *isobutyl alcohol*, and higher branched-chain alcohols. These are separated by fractional distillation.

*sec*-Butyl alcohol and *t*-butyl alcohol are obtained from olefins. Both 1-butene and 2-butene yield *sec*-butyl alcohol; isobutylene yields *t*-butyl alcohol.

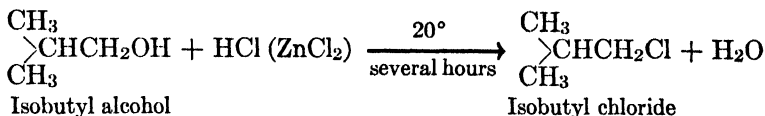
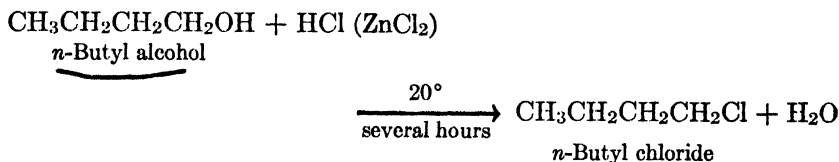
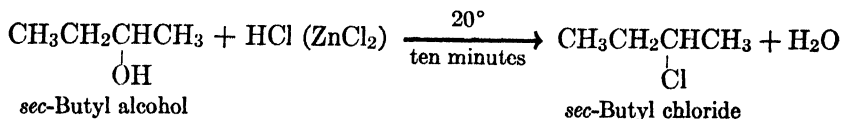
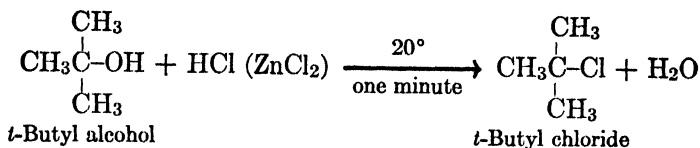


*n*-Butyl alcohol is prepared by the fermentation of starch or sugar in the presence of the bacterium *Clostridium acetobutylicum*. The process is usually known as the Weizmann fermentation, after the discoverer. The sugar may be obtained either as molasses or from corn. The products are *n*-butyl alcohol (60 per cent), acetone (30 per cent), and ethyl alcohol (10 per cent). These are separated by fractional distillation.

Another commercial synthesis of *n*-butyl alcohol employs acetaldehyde as the raw material (p. 225). Since acetaldehyde is obtained from







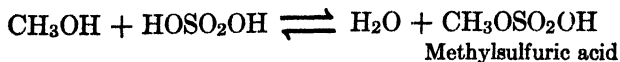
When this reaction is adapted to the preparation of primary chlorides it can be made to proceed more rapidly by raising the temperature.

Alkyl iodides can be prepared from alcohols and hydriodic acid, but the method below is more satisfactory.

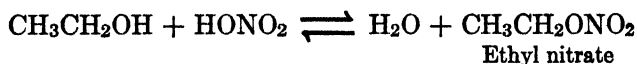
3. *With Phosphorus Halides.* Halides of phosphorus react with alcohols to give alkyl halides. Alkyl iodides are generally prepared by treating an alcohol with red phosphorus and iodine. The latter reagents combine to form phosphorus triiodide, which then converts the alcohol to the corresponding alkyl iodide. The synthesis of ethyl iodide from ethyl alcohol is an example.



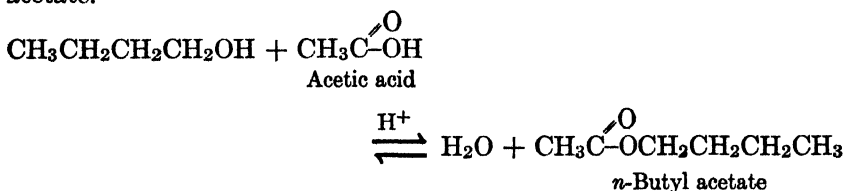
4. *With Oxygen Acids; Esterification.* Alcohols react with oxygen acids to form esters and water. The process is called esterification. When organic acids are employed a small amount of mineral acid is added as a catalyst. Methyl alcohol reacts with sulfuric acid to yield either methylsulfuric acid or methyl sulfate, depending on the conditions.



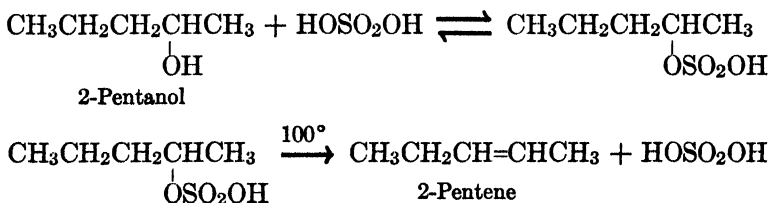
Ethyl alcohol and nitric acid form ethyl nitrate.



When acetic acid is esterified with *n*-butyl alcohol the product is *n* butyl acetate.

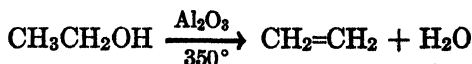


5. *Dehydration.* The removal of the elements of water from an alcohol is often a convenient method for the preparation of olefins. When simple alcohols are involved the sulfuric acid process (p. 17) is used. This is illustrated by the conversion of 2-pentanol into 2-pentene.

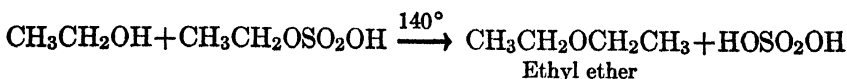
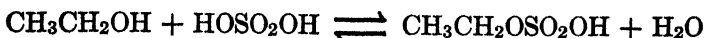


It is to be noted that the temperature employed in the above preparation is lower than that required in the case of ethylene (p. 17). In general, primary alcohols are most stable and tertiary alcohols are least stable to dehydrating agents; secondary alcohols are of intermediate stability.

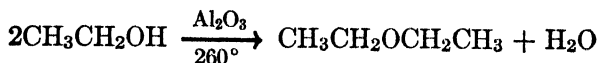
Other acids, such as potassium acid sulfate, phosphoric acid, or benzenesulfonic acid, can be used in place of sulfuric acid in the preparation of olefins from alcohols. Olefins may also be obtained by passing the vapor of an alcohol over a hot catalyst. Ethylene can be made from ethyl alcohol by this scheme.



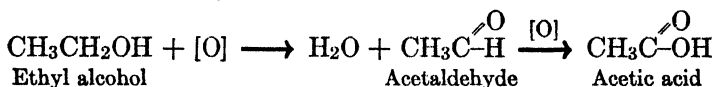
6. *Ether Formation.* Ethers are obtained by the removal of one molecule of water from two molecules of an alcohol. This is usually accomplished indirectly by converting part of the alcohol to the alkylsulfuric acid which is then heated while more of the alcohol is added. The synthesis of ethyl ether is illustrative.



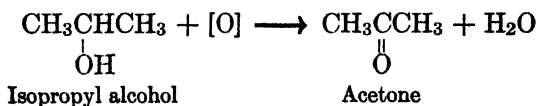
The same result can be achieved by vapor-phase dehydration of the alcohol in the presence of a catalyst.



7. *Oxidation.* Alcohols containing the group  $\begin{array}{c} \text{H} \\ | \\ -\text{C}-\text{OH} \end{array}$  are attacked by mild oxidizing agents. The process involves removal of the two hydrogen atoms, leaving the group  $\begin{array}{c} \text{H} \\ | \\ -\text{C}=\text{O} \end{array}$ . If a primary alcohol is used the resulting product is an aldehyde. Unless special precautions are taken the aldehyde is oxidized to an acid. Ethyl alcohol, for example, yields acetaldehyde and finally acetic acid.



Secondary alcohols are oxidized to ketones which are resistant to further oxidation. The simplest secondary alcohol, isopropyl alcohol, is converted to acetone.

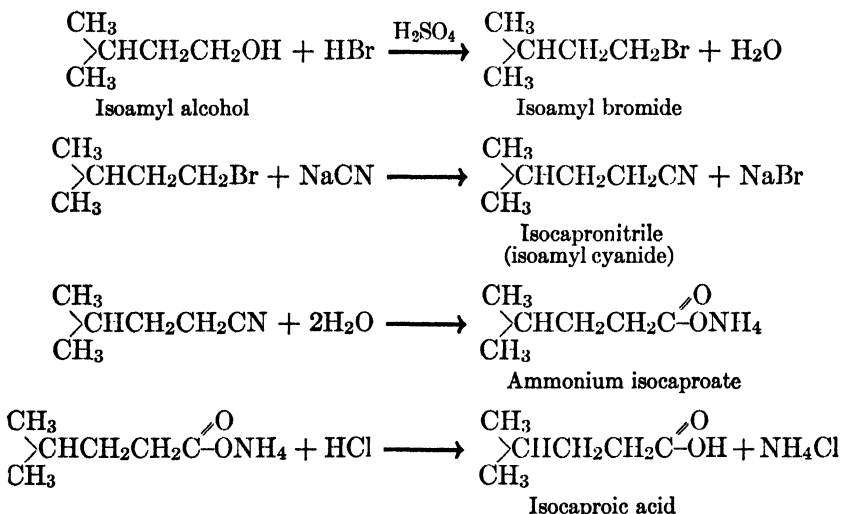


Tertiary alcohols do not contain the group  $\begin{array}{c} \text{H} \\ | \\ -\text{C}-\text{OH} \end{array}$  and hence cannot give a similar reaction. Actually it is found that their oxidation leads to the cleavage of the carbon chain.

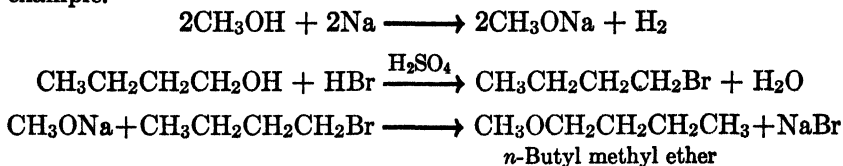
### The Use of Alkyl Halides in Synthesis

The reactions of alcohols, discussed above, are of value in the synthesis of other compounds, such as aldehydes, ketones, ethers, esters, and alkyl halides. Very often these substances are prepared for use as intermediates in further syntheses. This is true particularly of the alkyl halides; they undergo a variety of reactions and can be utilized in the synthesis of many types of compounds. Some of these transformations are listed below.

1. *With Alkali Cyanides.* Primary alkyl halides react metathetically with sodium or potassium cyanide. The organic cyanides so produced are generally known as nitriles. Their value depends chiefly on the fact that they can be hydrolyzed to acids. If the alkyl halide is prepared from an alcohol, the process amounts to the synthesis of an acid of one more carbon atom than the alcohol ( $\text{ROH} \longrightarrow \text{RCO}_2\text{H}$ ). This is exemplified by the transformation of isoamyl alcohol into isocaproic acid.

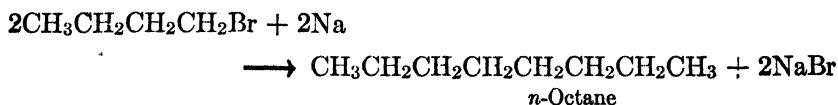


2. *With Sodium Alkoxides. The Williamson Synthesis of Ethers.* The synthesis of ethers from alcohols and sulfuric acid (p. 52) yields simple or symmetrical ethers of the type ROR. When a mixed or unsymmetrical ether, ROR', is desired, the Williamson synthesis is often used. The starting materials are usually the two alcohols ROH and R'OH. One of them is converted to the alkoxide by treatment with metallic sodium and the other is transformed to a halide. Interaction of these two reagents yields the unsymmetrical ether. The preparation of *n*-butyl methyl ether from methyl alcohol and *n*-butyl alcohol serves as an example.

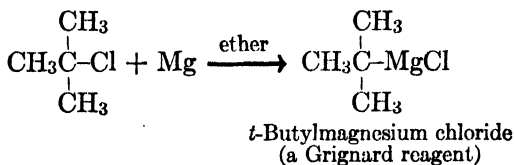


3. *With Alkali Metals. The Wurtz Synthesis of Paraffins.* An alkyl halide can be converted to a paraffin of twice the number of carbon atoms by reaction with metallic sodium. For example, a convenient

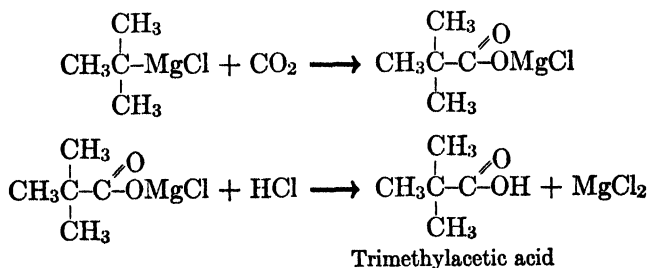
method of preparing *n*-octane involves a Wurtz reaction with *n*-butyl bromide.



4. *With Metallic Magnesium. Formation of Grignard Reagents.* In the presence of anhydrous ether, alkyl halides react with magnesium to form ether solutions of organomagnesium halides. Such a solution is known as a Grignard reagent, after the discoverer, the French chemist, Victor Grignard. An example is the formation of *t*-butylmagnesium chloride.



The Grignard reagents are very reactive substances and are employed in many syntheses. For example, the cyanide synthesis of acids from *tertiary* halides is unsuccessful, but these acids can be prepared by way of the Grignard reagents.



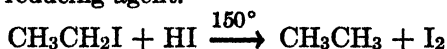
The use of the Grignard reagent in other synthetic methods will be mentioned frequently in subsequent chapters.

5. *With Sodium-Lead Alloy.* Organolead compounds are obtained from alkyl halides by treatment with sodium-lead alloy. The most important example is the commercial preparation of tetraethyllead.

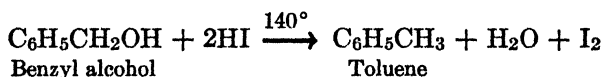


6. *With Reducing Agents.* The halogen atom of an alkyl halide can be replaced by a hydrogen atom by reduction. Sometimes a metal and an acid are used.

When an alkyl iodide is to be reduced, hydriodic acid is occasionally employed as the reducing agent.

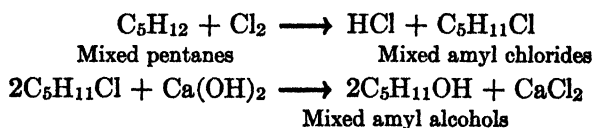


Since hydriodic acid converts alcohols to alkyl iodides, a variation of this method consists in treating an alcohol with excess hydriodic acid.

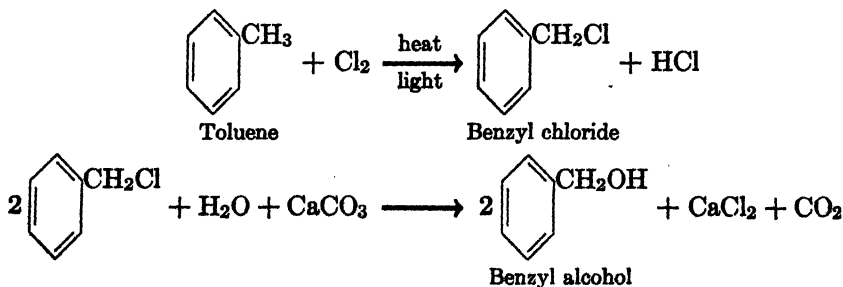


A further variation consists in treating an alcohol with red phosphorus, water, and a small amount of iodine or hydriodic acid. The phosphorus and iodine combine to give phosphorus iodide, which is hydrolyzed to phosphorous acid and hydriodic acid. The latter reacts with the alcohol to yield the iodide, and with the iodide to form the hydrocarbon and iodine. The iodine liberated at this stage reacts with more phosphorus and the cycle is repeated. Thus, only a trace of iodine or hydriodic acid need be employed.

7. *With Alkalies.* The dehydrohalogenation of alkyl halides by treatment with anhydrous alkali has been mentioned as a method for preparing olefins (p. 18). If aqueous alkali is used the alkyl halide undergoes hydrolysis, yielding an alcohol. The hydrolysis involves reversing the reaction by which alkyl halides are usually prepared, and in consequence, it is of value only in special cases where the halide is prepared from a raw material other than an alcohol. An important example is the commercial preparation of ethylene glycol (see next paragraph). The reaction is also utilized commercially in the preparation of a mixture of amyl alcohols by chlorinating pentanes and hydrolyzing the resulting amyl chlorides.

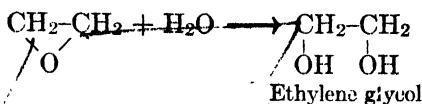
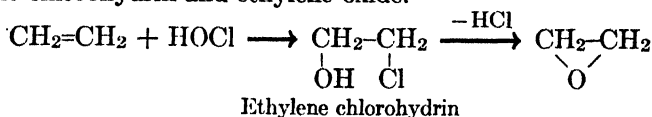


By the same method, benzyl alcohol can be obtained from toluene.



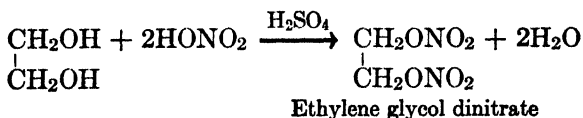
## Polyfunctional Alcohols

Alcohols containing two hydroxyl groups are known as glycols. The most important of this group of compounds is the simplest member, ethylene glycol. It is prepared commercially from ethylene by way of ethylene chlorohydrin and ethylene oxide.



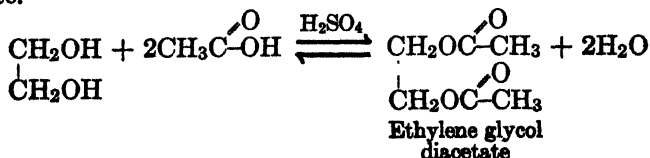
Ethylene glycol is a viscous liquid boiling at 197°. It has a sweet taste; indeed, the name glycol (*γλυκός*, sweet; *ol*, alcohol) derives from this fact. Most compounds containing several hydroxyl groups are extremely soluble in water; ethylene glycol and water are miscible in all proportions. Because of its high boiling point, its low solvent action on rubber and lacquers, and its solubility in water, ethylene glycol is widely used as an antifreeze for automobile radiators. In recent years it has come to prominence as the cooling liquid for airplane engines. One of its advantages over water in this connection is that it permits a higher operating temperature, which increases the efficiency of the engine.

Ethylene glycol has the chemical properties to be expected of an alcohol with two primary hydroxyl groups. The most common derivatives are its esters and ethers (p. 60). Esters are formed with both inorganic and organic acids. An example of the former type is the dinitrate.



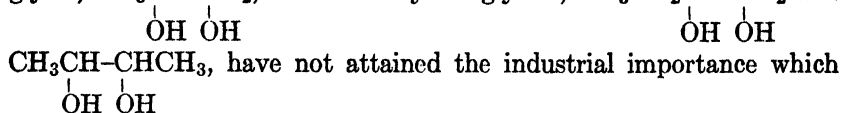
Ethylene glycol dinitrate bears a close structural relationship to nitroglycerine and like it is a powerful explosive. It is used extensively as an ingredient of dynamite (p. 58).

Esters of organic acids may be obtained by the methods used with simple alcohols. For example, acetic acid and the glycol form the diacetate.



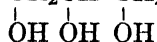


The glycols obtained from the higher olefins, such as propylene glycol,  $\text{CH}_3\text{CH}-\text{CH}_2$ , and the butylene glycols,  $\text{CH}_3\text{CH}_2\text{CH}-\text{CH}_2$  and

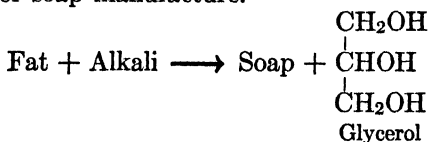


attaches to ethylene glycol. Glycols such as trimethylene glycol,  $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{OH}$ , and tetramethylene glycol,  $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ , are prepared by other methods.

Glycerol, or glycerine, is a trihydroxy alcohol of the formula  $\text{CH}_2\text{CH}-\text{CH}_2$ . It boils at  $290^\circ$  and is more viscous than ethylene

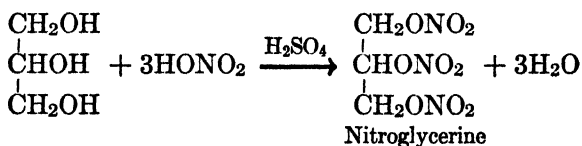


glycol. It is also completely miscible with water. Glycerol is obtained as a by-product of soap manufacture.



Because it takes up water from the air, glycerol finds many uses as a moistening agent. Its use in tobaccos depends on this property. Large quantities of glycerol are used by the rayon industry (p. 201). It is one of the raw materials for the preparation of resins for use in varnishes and enamels (p. 139).

Glyceryl trinitrate, or nitroglycerine, is made by the treatment of glycerol with nitric acid in the presence of sulfuric acid.



Nitroglycerine is one of the most powerful high explosives. It is a colorless liquid which freezes just above  $0^\circ$ . In the liquid state it is very sensitive to shock and so is dangerous to handle. It is generally used as dynamite, which consists of a porous material such as clay or sawdust impregnated with nitroglycerine and cast into sticks. In this form it is much less sensitive to shock and can be transported with little risk. When dynamite is subjected to temperatures below  $0^\circ$ , the nitroglycerine crystallizes and the dynamite becomes so stable that it does not respond to the detonation caps. Low-freezing dynamites are made with mixtures of nitroglycerine and ethylene glycol dinitrate (m.p.  $-20^\circ$ ). Ethylene glycol dinitrate is itself a more powerful explosive than nitroglycerine, so the efficiency of the dynamite is not lessened by such addition.

## The Ethers

Ethers are usually prepared by the action of sulfuric acid on alcohols (p. 52) or by the Williamson method (p. 54). The latter is employed when mixed ethers (ROR') are sought. The names and boiling points of a few ethers are given in Table X.

TABLE X  
TABLE OF ETHERS

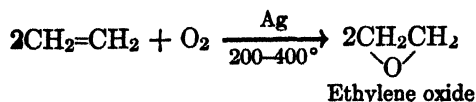
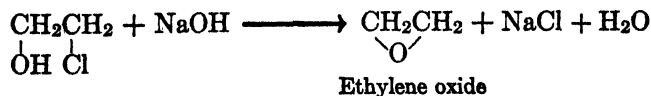
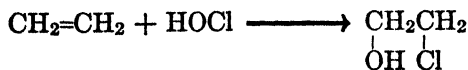
Name	Formula	Boiling Point	Class
Methyl ether	$\text{CH}_3\text{OCH}_3$	$-24^\circ$	Aliphatic
Methyl ethyl ether	$\text{CH}_3\text{OCH}_2\text{CH}_3$	10	Mixed, aliphatic
Ethyl ether	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	35	Aliphatic
<i>n</i> -Butyl ether	$\text{C}_4\text{H}_9\text{OC}_4\text{H}_9$	142	Aliphatic
Anisole (methyl phenyl ether)	$\text{CH}_3\text{OC}_6\text{H}_5$	155	Mixed
Phenyl ether	$\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$	259	Aromatic
Phenyl <i>p</i> -tolyl ether	$\text{C}_6\text{H}_5\text{OC}_6\text{H}_4\text{CH}_3$	278	Mixed, aromatic

The most common of these is ethyl ether, ordinarily known simply as ether. It is the most widely used general anesthetic. It is an excellent solvent for many organic compounds and is used in industry and in the laboratory in this connection.

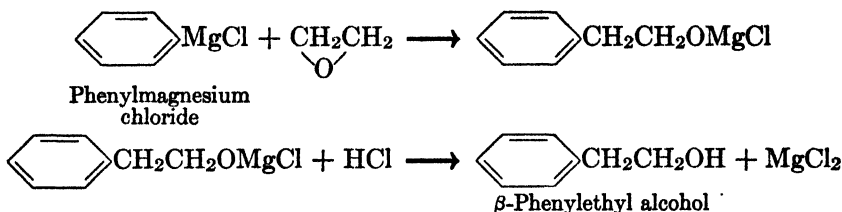
The ordinary ethers are inert toward most reagents. They can be cleaved by halogen acids. For example, ethyl ether is converted to ethyl bromide by the action of excess concentrated hydrobromic acid.



Ethylene oxide is a cyclic ether of unusual interest. It is prepared by the action of alkali on ethylene chlorohydrin or by the controlled oxidation of ethylene (p. 21).

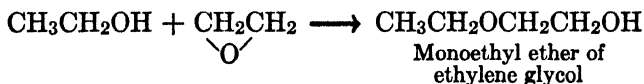


Ethylene oxide is much more reactive than are the simple open-chain ethers. For example, although ethyl ether is so inert toward Grignard reagents that it is employed as the solvent in their preparation, ethylene oxide reacts readily with these compounds.  $\beta$ -Phenylethyl alcohol, a constituent of attar of roses, is made commercially by this method.



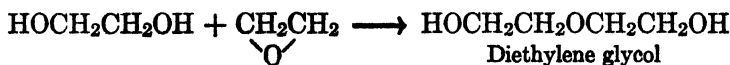
This reaction is often employed in synthetic work as a process for lengthening carbon chains. By converting the alcohol to the bromide and repeating the synthesis it is possible to build up carbon chains of any desired length;  $\text{RBr} \longrightarrow \text{RCH}_2\text{CH}_2\text{OH} \longrightarrow \text{RCH}_2\text{CH}_2\text{Br} \longrightarrow \text{RCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ , etc.

Ethylene oxide reacts with alcohols to give monoethers of ethylene glycol.

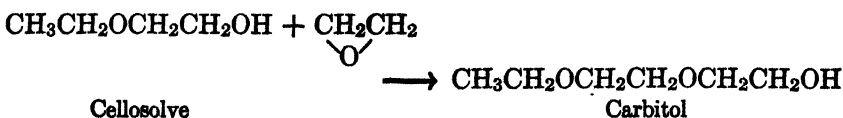


The product from ethyl alcohol is sold under the name cellosolve for use as a solvent. Other similar solvents are methylcellosolve,  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ , and butylcellosolve,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ , obtained from the oxide and methyl and *n*-butyl alcohols, respectively.

When ethylene oxide is allowed to react with ethylene glycol the product is diethylene glycol.

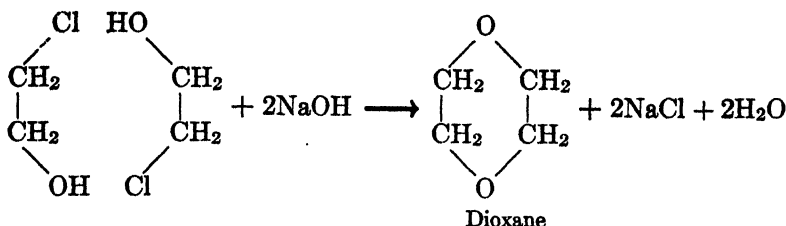


By employing cellosolve in this reaction carbitol is obtained.



Methylcarbitol and butylcarbitol are produced from the corresponding cellosolves.

Ethylene oxide may be regarded as the monomolecular ether of ethylene glycol. A by-product obtained in its preparation is dioxane, the bimolecular ether of the glycol.



Dioxane is also obtained from the glycol by the ordinary sulfuric acid process.

## MERCAPTANS (THIO ALCOHOLS) AND SULFIDES (THIO ETHERS)

### Mercaptans

From the close relationship of oxygen and sulfur in the periodic table it might be expected that substances analogous to alcohols, but containing sulfur instead of oxygen, could be prepared. Such compounds are well known. The simplest is methyl mercaptan,  $\text{CH}_3\text{SH}$ . The names and boiling points of a few members of this series are given in Table XI. The systematic names of these compounds are derived in the same manner as those of the alcohols, the name ending being *thiol*.

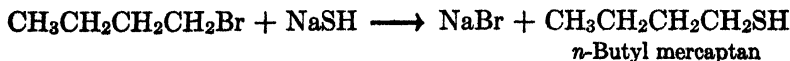
TABLE XI

#### MERCAPTANS

Name	Formula	Boiling Point
Methyl mercaptan (methanethiol)	$\text{CH}_3\text{SH}$	6°
Ethyl mercaptan (ethanethiol)	$\text{CH}_3\text{CH}_2\text{SH}$	37
<i>n</i> -Propyl mercaptan (1-propanethiol)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{SH}$	68
Isopropyl mercaptan (2-propanethiol)	$\text{CH}_3\text{CH}(\text{SH})\text{CH}_3$	60
<i>n</i> -Butyl mercaptan (1-butanethiol)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SH}$	98

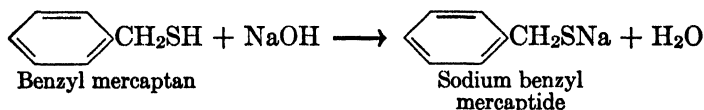
It will be noted that the mercaptans have lower boiling points than the corresponding alcohols, although their molecular weights are greater. This indicates that they do not associate as do the alcohols (p. 45).

Mercaptans are usually prepared from an alkyl halide and sodium hydrosulfide. Thus *n*-butyl mercaptan is formed from *n*-butyl bromide and sodium hydrosulfide.



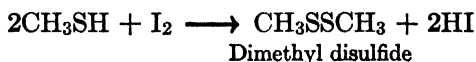
This reaction may be compared to the formation of an alcohol from an alkyl halide and sodium hydroxide.

A comparison of the chemical properties of mercaptans and alcohols reveals more contrasts than similarities. For example, the mercaptans are weak acids, whereas alcohols are neutral. Benzyl mercaptan reacts with sodium hydroxide to give the corresponding salt, sodium benzyl mercaptide.



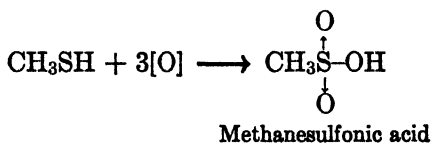
The acidity of the mercaptans is in harmony with the view that they are the alkyl derivatives of hydrogen sulfide, which is an acid. The alcohols may be considered as the alkyl derivatives of water.

The behavior of mercaptans toward oxidizing agents is altogether different from that of the alcohols. A mild oxidizing agent removes the hydrogen atom of the functional group, giving rise to a disulfide. The oxidation may be brought about by iodine, hydrogen peroxide, hypoiodite solutions, or even the oxygen of the air. Iodine, for example, converts methyl mercaptan to dimethyl disulfide.



This reaction is quantitative and can be used for the analytical determination of mercaptans. The mercaptan can be regenerated by reduction of the disulfide.

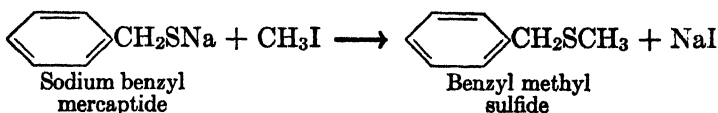
Strong oxidizing agents convert mercaptans to sulfonic acids. Methyl mercaptan, for example, yields methanesulfonic acid.



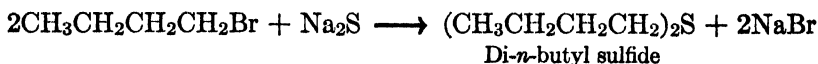
This reaction is sometimes used for the preparation of aliphatic sulfonic acids.

### Sulfides

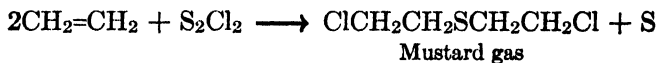
The sulfides show as little resemblance to ethers, so far as chemical properties are concerned, as do the mercaptans to the alcohols. The sulfides are usually prepared from mercaptides and alkyl halides. An example is the preparation of benzyl methyl sulfide from sodium benzyl mercaptide and methyl iodide.



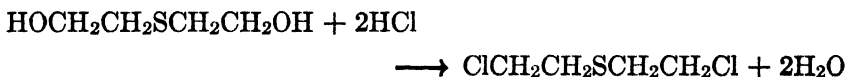
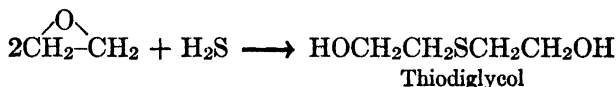
A modification employed in the preparation of symmetrical sulfides consists in treating an alkyl halide with sodium sulfide. Sodium sulfide acts upon *n*-butyl bromide to give di-*n*-butyl sulfide.



The best-known sulfide is  $\beta,\beta'$ -dichlorodiethyl sulfide, or mustard gas. It is prepared from ethylene and sulfur chloride.

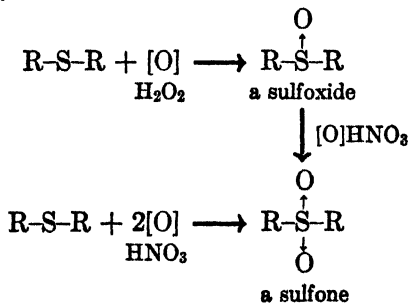


Another method employs ethylene oxide and hydrogen sulfide. The primary product is thiodiglycol, which is converted to mustard gas by hydrochloric acid.



Mustard gas is a powerful vesicant; it penetrates the skin without causing any immediate pain but within a short time deep blisters, which heal very slowly, form on the exposed area. The name mustard gas is misleading. The substance is a liquid boiling at 215°. Because of its high boiling point it evaporates very slowly, and a sector which has been subjected to a mustard gas attack remains hazardous for many days.

The sulfides are easily oxidized, taking up one or two atoms of oxygen. Mild oxidizing agents convert them to sulfoxides, which can be further oxidized to sulfones.



## PROBLEMS

1. Write equations for the transformation of *n*-amyl alcohol into: (a) *n*-amyl bromide, (b) *n*-amyl ether, (c) ethyl *n*-amyl ether, (d) 1-pentene, (e) 2-pentanol, (f) *n*-valeraldehyde ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$ ), (g) *n*-valeric acid, (h) *n*-pentane, (i) *n*-amyl mercaptan, (j) *n*-amyl acetate, (k) *n*-amylcellosolve, (l) *n*-amylcarbitol, (m) *n*-amyl disulfide, (n) *n*-amyl sulfide, (o) 1-pentanesulfonic acid, (p) *n*-heptyl alcohol.
- ✓ 2. Write the formulas of the following alcohols, indicate their classes, and name them according to the Geneva system: (a) *n*-amylcarbinol, (b) isoamylcarbinol, (c) methylisobutylcarbinol, (d) neopentylcarbinol, (e) methyldiethylcarbinol, (f) benzylcarbinol.
- ✓ 3. Write equations for the commercial preparations of methyl alcohol, ethyl alcohol, the propyl alcohols, and the butyl alcohols.

## SUGGESTED READINGS

- KILLEFFER, "Butanol and Acetone from Corn," *Ind. Eng. Chem.*, **19**, 46 (1927).  
LEVEY, "The Production and Economics of Synthetic Glycerol," *Ind. Eng. Chem., News Ed.*, **16**, 326 (1938).  
BACKHAUS, "Ethyl Alcohol," *Ind. Eng. Chem.*, **22**, 1151 (1930).

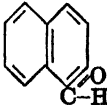
# CHAPTER VIII

## ALDEHYDES AND KETONES

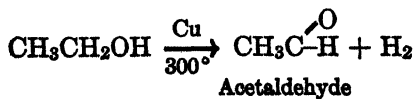
### The Aldehydes

Those compounds containing the group  $\text{--}\overset{\text{O}}{\text{C}}\text{--H}$  are known as aldehydes. The name originated from the consideration that the compounds are obtained from primary alcohols by dehydrogenation (*alcohol dehydrogenatum*). The common aldehydes are named with reference to the acids which they yield on oxidation. The Geneva system employs the ending *al*. Examples are given in Table XII.

TABLE XII  
ALDEHYDES

Name	Formula	Boiling Point	Name of the Corresponding Acid
Formaldehyde (methanal)	$\text{HC}\overset{\text{O}}{\text{--H}}$	$-21^{\circ}$	Formic
Acetaldehyde (ethanal)	$\text{CH}_3\text{C}\overset{\text{O}}{\text{--H}}$	20.2	Acetic
Propionaldehyde (propanal)	$\text{CH}_3\text{CH}_2\text{C}\overset{\text{O}}{\text{--H}}$	48.8	Propionic
<i>n</i> -Butyraldehyde (butanal)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}\overset{\text{O}}{\text{--H}}$	75.7	Butyric
Benzaldehyde	$\text{C}_6\text{H}_5\text{C}\overset{\text{O}}{\text{--H}}$	179.5	Benzoic
<i>p</i> -Tolualdehyde	$\text{CH}_3\text{--}\langle\text{C}_6\text{H}_4\rangle\text{--C}\overset{\text{O}}{\text{--H}}$	204	<i>p</i> -Toluic
$\alpha$ -Naphthaldehyde		291.6	$\alpha$ -Naphthoic

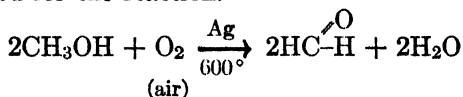
**The Preparation of Aldehydes.** 1. As indicated above, aldehydes may be obtained from primary alcohols. In one of the commercial processes for acetaldehyde, catalytic dehydrogenation is used.





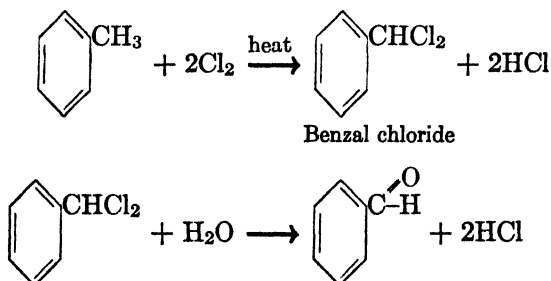
The industrial preparation of acetaldehyde by the hydration of acetylene has been mentioned elsewhere (p. 23).

In laboratory preparations it is frequently more convenient to employ an oxidizing agent. Although the aldehydes are more easily oxidized than the alcohols the process can be made successful by operating at temperatures above the boiling point of the aldehyde, but below that of the alcohol. Another adaptation of the use of an oxidizing agent is the air oxidation of methyl alcohol by passing it through a hot silver gauze; some air is admitted to burn a part of the hydrogen and thus produce the heat required for the reaction.



This method is used commercially for the preparation of formaldehyde.

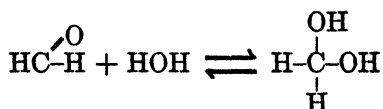
2. The hydrolysis of 1,1-dihalides is often a convenient method for the preparation of aromatic aldehydes. For example, benzaldehyde is obtained from toluene by the following reactions.



The second step is carried out in the presence of an alkali or carbonate which neutralizes the hydrochloric acid.

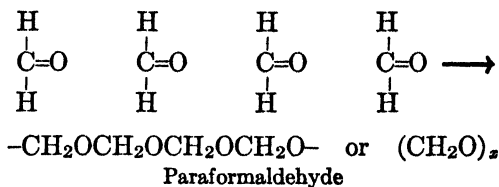
There are a number of other methods for the preparation of aldehydes; a more extensive discussion will be found in Chapter XXI.

**Formaldehyde.** Formaldehyde is a colorless gas of very irritating odor. It is a strong poison, and has been used as a disinfectant and as a fumigant. It is usually sold as a 40 per cent aqueous solution under the name formalin. The stability of this solution indicates that it may contain the hydrate of formaldehyde (p. 300).



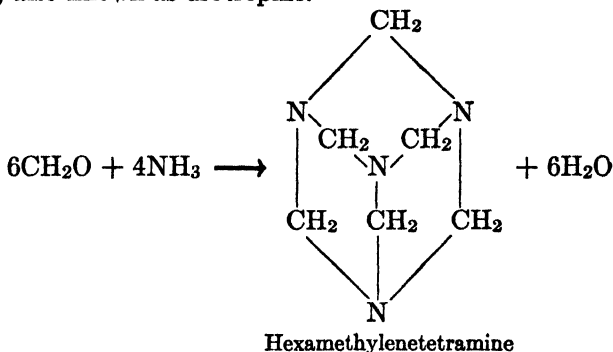
Formaldehyde is also transported and sold as the solid polymer, para-formaldehyde, which can be obtained by evaporation of formalin. The

polymerization involves self-addition of many molecules of formaldehyde.

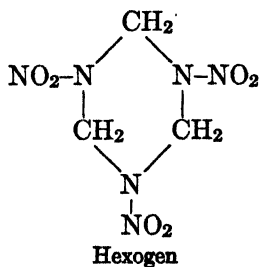


Paraformaldehyde undergoes depolymerization when it is heated, forming gaseous formaldehyde. When the latter is desired in the laboratory it is usually obtained in this way. The use of "formaldehyde candles" in fumigation is another application of this process. The candle is paraformaldehyde which is depolymerized over a miniature alcohol stove.

Formaldehyde reacts with ammonia to give hexamethylenetetramine,  $(\text{CH}_2)_6\text{N}_4$ , also known as urotropine.



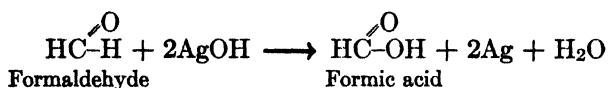
When hexamethylenetetramine is taken internally it is hydrolyzed in the kidney and is eliminated as formaldehyde. It is used in medicine as a urinary disinfectant. It is also employed as a catalyst in the vulcanization of rubber. Treatment with 96 per cent nitric acid at  $0^\circ$  converts hexamethylenetetramine into trimethylenetrinitroamine, which is known as Hexogen and is a high explosive resembling Tetryl (p. 379).



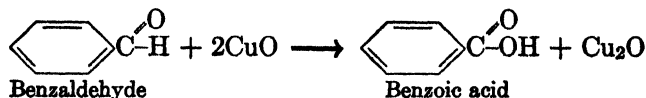
The most important uses of formaldehyde at the present time are in the preparation of plastics (pp. 126, 163).

**The Higher Aldehydes.** The reactions of formaldehyde discussed above are peculiar to it. In addition it undergoes a number of reactions which are also characteristic of the other aldehydes. These are discussed below.

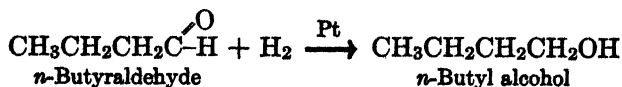
1. *Oxidation.* Perhaps the outstanding property of aldehydes is the ease with which they are oxidized to acids. Such mild oxidizing agents as alkaline solutions containing silver or copper salts suffice to bring about the reaction. If a silver salt is to be used it is first dissolved in an excess of ammonium hydroxide. The resulting solution, known as Tollens' reagent, deposits metallic silver when an aldehyde is added. If the reaction is carried out in scrupulously clean glassware the silver forms a mirror on the walls of the vessel. This reaction is widely used as a laboratory test for aldehydes; it is known as the *Tollens' test* or as the *silver mirror test*. The following equation represents the reaction for formaldehyde.



The Fehling test and the Benedict test differ in that a copper salt is employed. Alkaline solutions containing a cupric salt and salts of certain organic acids are stable, although cupric hydroxide is insoluble in water. Fehling's solution contains potassium sodium tartrate (p. 142) and Benedict's solution contains sodium citrate (p. 142). When an aldehyde is added the copper is reduced and separates as cuprous oxide. For convenience in writing equations the reagents may be considered as containing cupric oxide.

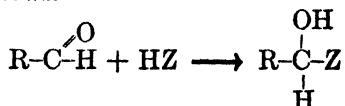


2. *Reduction.* The dehydrogenation of primary alcohols to aldehydes is a reversible process. By treating an aldehyde with hydrogen in the presence of a catalyst such as platinum or nickel the primary alcohol can be obtained in good yields. Thus *n*-butyraldehyde, normally made from *n*-butyl alcohol by dehydrogenation, can be reconverted to it by hydrogenation.

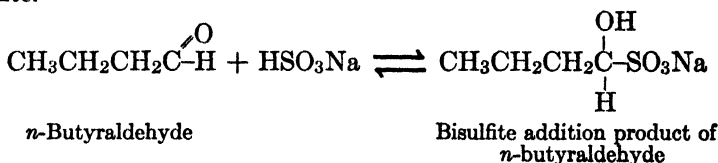


Chemical reducing agents, such as iron and acetic acid, also may be used to transform an aldehyde to a primary alcohol.

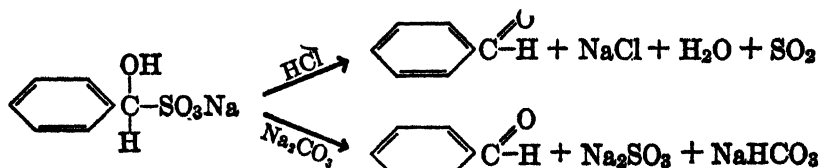
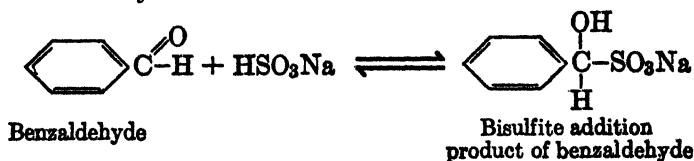
3. *Addition of Reagents Containing Active Hydrogen Atoms.* Aldehydes react with sodium bisulfite, hydrogen cyanide, alcohols, and, in some cases, ammonia. All the reactions are alike in that the carbonyl group of the aldehyde undergoes addition of the reagent. The hydrogen atom of the reagent goes to the oxygen atom, and the remainder of the reagent to the carbon atom, of the carbonyl group. The general scheme may be represented as follows.



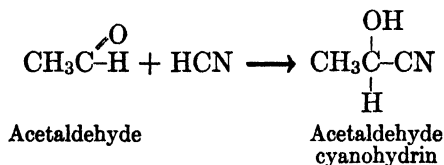
The sodium bisulfite addition products of aldehydes are obtained when the aldehyde, sometimes in alcohol solution, is added to aqueous sodium bisulfite.



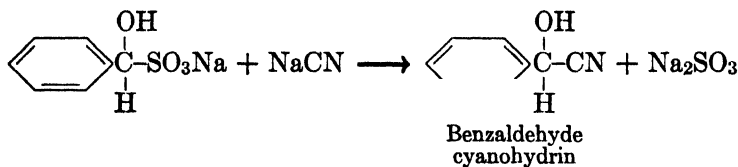
Since these addition products are salts, their solubilities are greatly different from those of the aldehydes. Because of this they are sometimes very useful in purifying aldehydes. For instance, if benzaldehyde (b.p. 179.5°) were prepared in the laboratory by the dehydrogenation of benzyl alcohol (b.p. 205°) the crude product would probably contain some of the unchanged alcohol. Purification could be effected by treating the material with sodium bisulfite solution and adding alcohol to precipitate the addition product. The latter, being a salt, is insoluble in ether and can be washed free of benzyl alcohol with this solvent. Treatment of the purified addition product with either acid or base regenerates benzaldehyde.



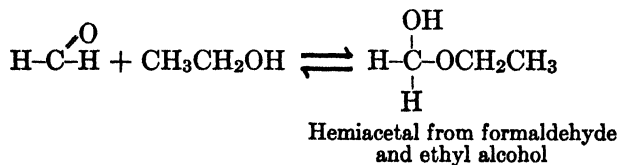
*Cyanohydrins*, compounds containing both a cyano group and a hydroxyl group, are obtained from aldehydes and hydrocyanic acid. That from acetaldehyde may be taken as an example.



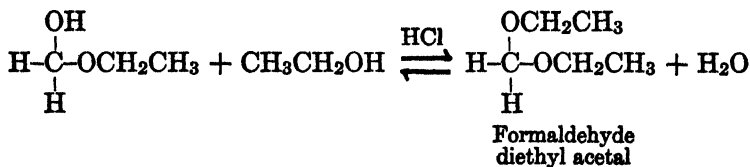
Cyanohydrins are used in the synthesis of substituted acids (pp. 141, 307). Because hydrocyanic acid is a poisonous gas the cyanohydrins are usually made indirectly by treating a bisulfite addition product with sodium or potassium cyanide. Sodium cyanide and the bisulfite addition compound of benzaldehyde react according to the following scheme.



A *hemiacetal* is formed when an aldehyde and an alcohol are brought together. Hemiacetals are ordinarily unstable and decompose to the aldehyde and alcohol during attempted isolation. Formaldehyde and ethyl alcohol are believed to react in this manner.

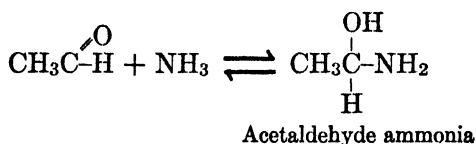


In the presence of a trace of mineral acid the hemiacetal reacts with another molecule of alcohol, by elimination of a molecule of water, forming an *acetal*. The acetals are stable under ordinary conditions. In the presence of acid and water they revert to aldehydes and alcohols. This is illustrated by the reversible formation of the diethyl acetal of formaldehyde.



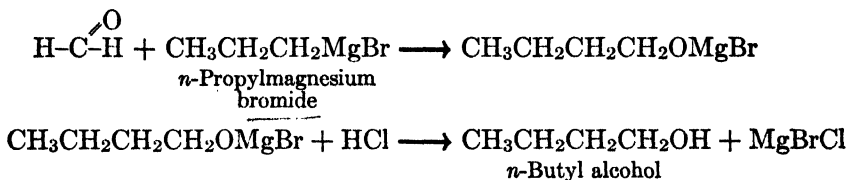
If a mercaptan is used instead of an alcohol the sulfur analog of the acetal is obtained. These substances are called mercaptals.

*Ammonia* yields unstable addition products with aliphatic aldehydes other than formaldehyde (p. 67). Acetaldehyde is often collected by passing it into ammonium hydroxide. The solid aldehyde ammonia which is formed can be reconverted to the aldehyde by treatment with dilute acids.



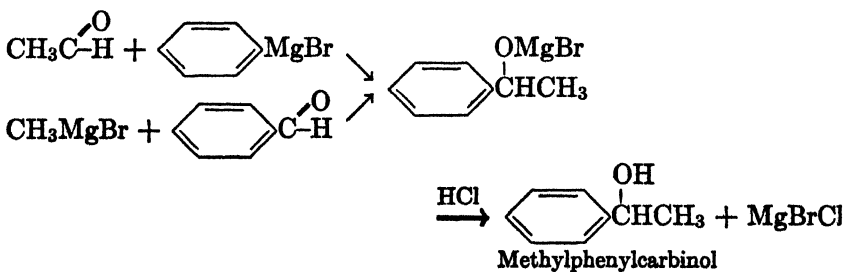
Aromatic aldehydes and ammonia react in a different manner (p. 303).

4. *Addition of the Grignard Reagent.* The Grignard reagent adds to the carbonyl groups of aldehydes with the formation of derivatives of alcohols. With formaldehyde a primary alcohol is obtained. *n*-Butyl alcohol can be made in this way from *n*-propyl bromide.



It will be noted that the primary alcohol produced contains one more carbon atom than the Grignard reagent. The process thus enables one to convert an alcohol to the corresponding primary alcohol of one additional carbon atom;  $\text{ROH} \longrightarrow \text{RBr} \longrightarrow \text{RMgBr} \longrightarrow \text{RCH}_2\text{OH}$  (p. 55).

All other aldehydes yield derivatives of secondary alcohols upon treatment with a Grignard reagent. Methylphenylcarbinol may be obtained either from acetaldehyde and phenylmagnesium bromide or from benzaldehyde and methylmagnesium bromide.



The preparation of secondary alcohols from aldehydes and Grignard reagents is a valuable synthetic method. As in the above case, the secondary alcohol  $\text{RCH}(\text{OH})\text{R}'$  can be prepared from two sets of reagents.

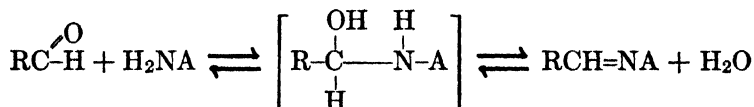


The group  $\text{CHOH}$  is generated from the carbonyl group of the aldehyde; R may be the alkyl group of the Grignard reagent and R' that of the aldehyde, or R may be the alkyl group of the aldehyde and R' that of the Grignard reagent. Whether the secondary alcohol  $\text{RCH}(\text{OH})\text{R}'$  is made

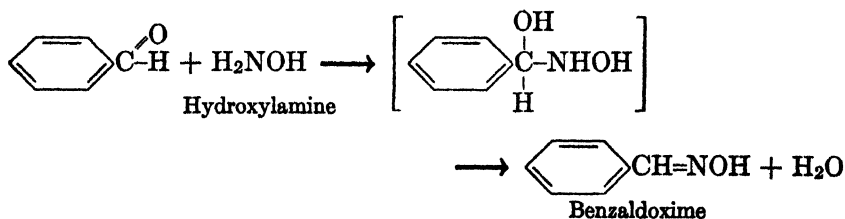


from  $\text{RMgX}$  and  $\text{R}'\text{C}(=\text{O})\text{H}$  or from  $\text{R}'\text{MgX}$  and  $\text{RC}(=\text{O})\text{H}$  will usually depend on the availability of the various reagents.

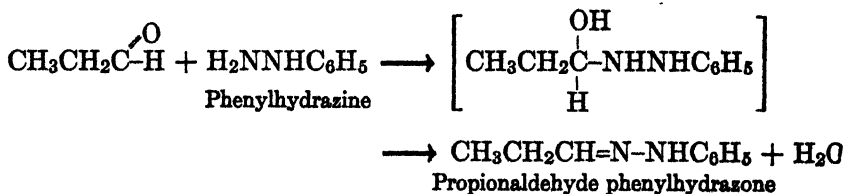
5. *Condensation with Hydroxylamine and Derivatives of Hydrazine.* Certain derivatives of ammonia form unstable addition products with aldehydes. These addition products lose the elements of water to form compounds containing a double bond between carbon and nitrogen. The general scheme for reactions of this type is as follows.



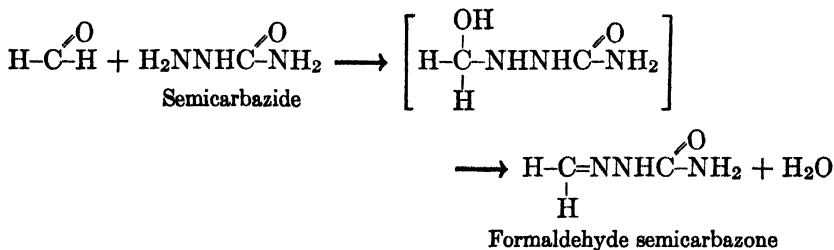
The reaction of aldehydes with hydroxylamine leads to the formation of *oximes*. Benzaldoxime is synthesized in this way.



If phenylhydrazine is employed the product is a phenylhydrazone. Propionaldehyde forms a typical phenylhydrazone.

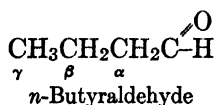


With semicarbazide, semicarbazones are obtained. This reaction has been carried out with formaldehyde, for example.



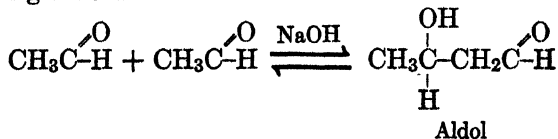
The oximes, phenylhydrazones, and semicarbazones are of value in the identification of carbonyl compounds because they are usually easily purified solids of definite melting points. Phenylhydrazine is particularly useful as a reagent for sugars (p. 192).

6. *Reactions of Aldehydes in the Presence of Alkali.* Aldehydes may be separated into two classes according to their behavior in the presence of alkali. The basis of the separation lies in the reactivity of the hydrogen atoms attached to the carbon adjacent to the carbonyl group. This carbon atom is usually called the  $\alpha$ -carbon. The use of the Greek letters in this sense is illustrated with *n*-butyraldehyde.



The  $\alpha$ -carbon atom is the one to which the functional group is attached. When the functional group is a carbonyl group the hydrogen atoms on the  $\alpha$ -carbon atom are very reactive. This activation does not extend to the hydrogen atoms on the  $\beta$ - and  $\gamma$ -carbon atoms; these appear to have very little more reactivity than the hydrogen atoms in *n*-butane.

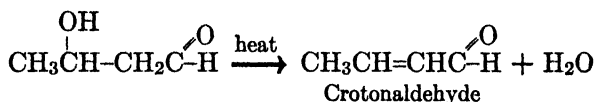
*The aldol condensation.* Aldehydes which have a hydrogen atom on the  $\alpha$ -carbon atom undergo self-addition in the presence of alkali. Thus, acetaldehyde gives aldol.



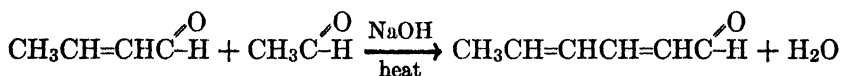
The reaction closely resembles the other additions of the aldehydes. A hydrogen atom of the second molecule attaches to the oxygen atom, and the remainder to the carbon atom of the carbonyl group of the first molecule.



Aldol contains a hydroxyl group and an active hydrogen atom on adjacent carbon atoms. These can be removed easily, either by heating or by treatment with a dehydrating agent, to give crotonaldehyde.

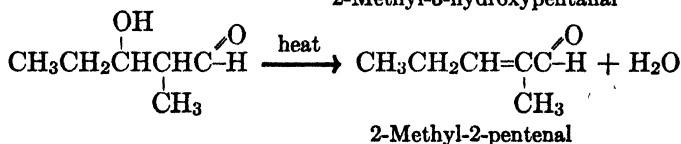
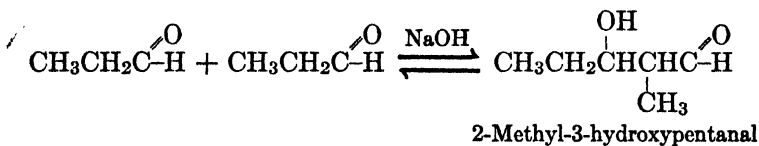


If crotonaldehyde is desired, aldol is prepared under mild conditions and then dehydrated. If a mixture of acetaldehyde and sodium hydroxide solution is heated, the crotonaldehyde reacts with acetaldehyde.



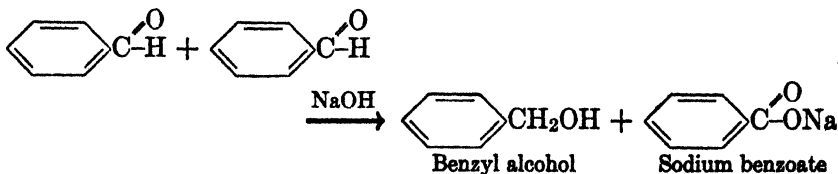
The process can be repeated indefinitely, so that a mixture of colored products of high molecular weight will result; these are the *aldehyde resins*.

Since the aldol condensation involves the hydrogen atom of the  $\alpha$ -carbon atom, the homologs of acetaldehyde give branched-chain aldols. Propionaldehyde yields 2-methyl-3-hydroxypentanal.

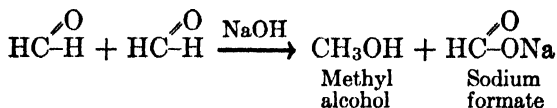


A remarkable feature of the aldol condensation is that it is reversible.

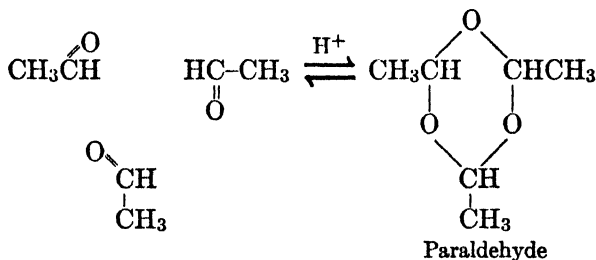
*The Cannizzaro reaction.* Aldehydes which have no hydrogen atom on the  $\alpha$ -carbon atom obviously cannot give the aldol condensation. They do react in the presence of alkali, however. In such cases an oxidation-reduction reaction occurs. Benzaldehyde, for example, is converted to benzyl alcohol and sodium benzoate.



The net result of the Cannizzaro reaction is that one molecule of the aldehyde is reduced to the primary alcohol and the other is oxidized to the acid (produced as the sodium salt). This reaction is characteristic of aromatic aldehydes since these cannot have a hydrogen atom on the  $\alpha$ -carbon atom. Certain aliphatic aldehydes also give the same reaction, notably formaldehyde,  $\text{H}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{H}$ .



7. *Polymerization.* Although formaldehyde readily changes to a solid polymer (p. 66), its homologs yield high polymers only under the influence of peroxidic catalysts and high pressures. However, they do form trimers readily; when acetaldehyde is treated with a trace of acid it changes to paraldehyde.



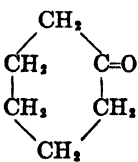
In the pure state paraldehyde is stable, but if it is warmed with a trace of mineral acid acetaldehyde is generated. When acetaldehyde is desired in the laboratory it is made from paraldehyde in this way.

### The Ketones

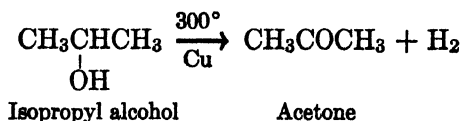
The ketones, as was noted earlier (p. 6), contain a carbonyl group attached to two organic residues,  $\text{R}-\overset{\text{O}}{\text{C}}-\text{R}$ . Acetone, the simplest member of the series, has been known for nearly three centuries. It derives its name from the fact that it can be obtained from acetic acid. The other simple ketones are usually named with reference to the radicals attached to the carbonyl group. In the Geneva system the ending *one* is employed. The use of both systems is shown in Table XIII.

**Preparation of Ketones.** Ketones may be obtained from secondary alcohols by either oxidation or catalytic dehydrogenation. In industry the latter process is used. Acetone, for example, is obtained

TABLE XIII  
 SIMPLE KETONES

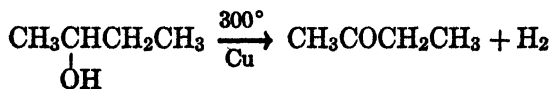
Name	Formula	Boiling Point
Acetone (propanone)	$\text{CH}_3\text{C}(=\text{O})\text{CH}_3$	56.1°
Methyl ethyl ketone (butanone)	$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_3$	79.6
Diethyl ketone (3-pentanone)	$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	101.7
Methyl <i>n</i> -propyl ketone (2-pentanone)	$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$	101.7
Isopropyl methyl ketone (methylbutanone)	$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2$	93
Cyclohexanone		156.7
Acetophenone (methyl phenyl ketone)	$\text{CH}_3\text{C}(=\text{O})\text{C}_6\text{H}_5$	202.3
Benzophenone (diphenyl ketone)	$\text{C}_6\text{H}_5\text{C}(=\text{O})\text{C}_6\text{H}_5$	306.0

from isopropyl alcohol. Since isopropyl alcohol is prepared from propylene, acetone may be regarded as a petroleum product.



This is not the only commercial source of acetone. As mentioned earlier (p. 49) it is obtained along with *n*-butyl alcohol in the Weizmann fermentation.

Methyl ethyl ketone is prepared by the dehydrogenation of *sec*-butyl alcohol.

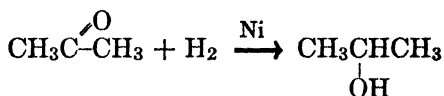


Acetone is produced in large quantities for use as a solvent in nitrocellulose processing and as a raw material in the preparation of drugs, such as iodoform (p. 9) and sulfonal (p. 78), and synthetic plastics (p. 146). Similar uses of methyl ethyl ketone are appearing.

Ketones are prepared in the laboratory by a number of different methods. These are discussed in Chapter XXI.

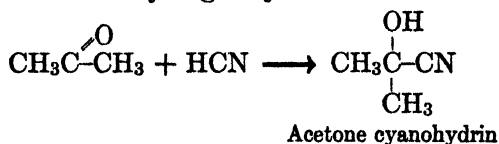
**Reactions of Ketones.** Since both aldehydes and ketones contain the carbonyl group they have many chemical properties in common. There are, however, a number of differences between the two classes. Ketones are most sharply differentiated from aldehydes in their resistance to oxidation. Reagents such as Tollens', Benedict's, or Fehling's solution have no effect on simple ketones.

1. *Reduction.* Reduction under mild conditions converts ketones to secondary alcohols. This is the reverse of the reaction by which ketones are prepared from alcohols. Catalytic hydrogenation or chemical reduction may be employed. In the presence of nickel, for example, hydrogen combines with acetone to yield isopropyl alcohol.

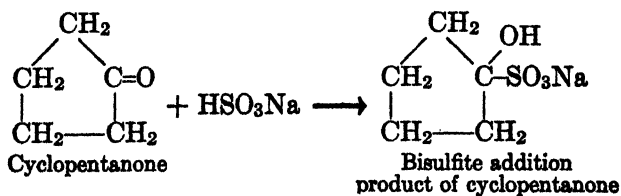


2. *Addition Reactions of Methyl Ketones and Cyclic Ketones.* The reactivity of ketones appears to be conditioned by the size of the organic residues attached to the carbonyl group. Aliphatic ketones containing

the grouping  $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{CH}_3$  are sufficiently reactive to undergo addition of sodium bisulfite or hydrogen cyanide. Acetone readily forms a cyanohydrin when treated with hydrogen cyanide.

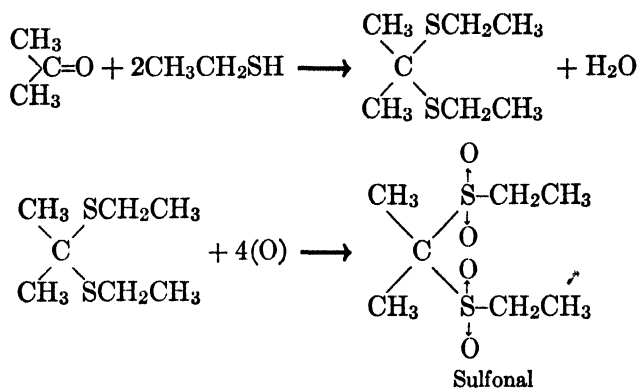


Cyclic ketones have about the same reactivity as methyl ketones. Cyclopentanone may be converted to a bisulfite addition compound.

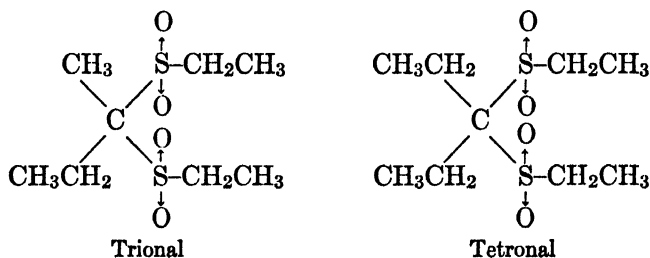


Ammonia and alcohols do not form addition products even with methyl ketones. Mercaptans, however, react readily.

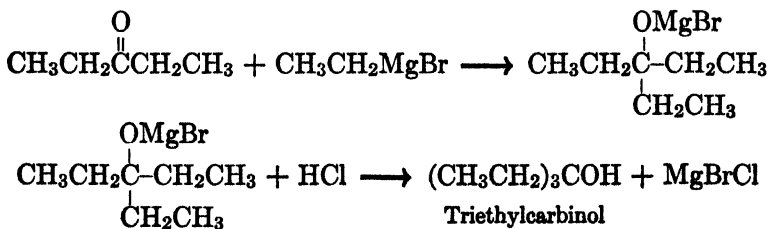
3. *Formation of Mercaptoles.* Aliphatic ketones react with mercaptans to give mercaptoles. Certain of these are intermediates in the preparation of drugs. Sulfonal is obtained from acetone as follows.



By the same reactions Trional is prepared from methyl ethyl ketone and Tetronal from diethyl ketone.



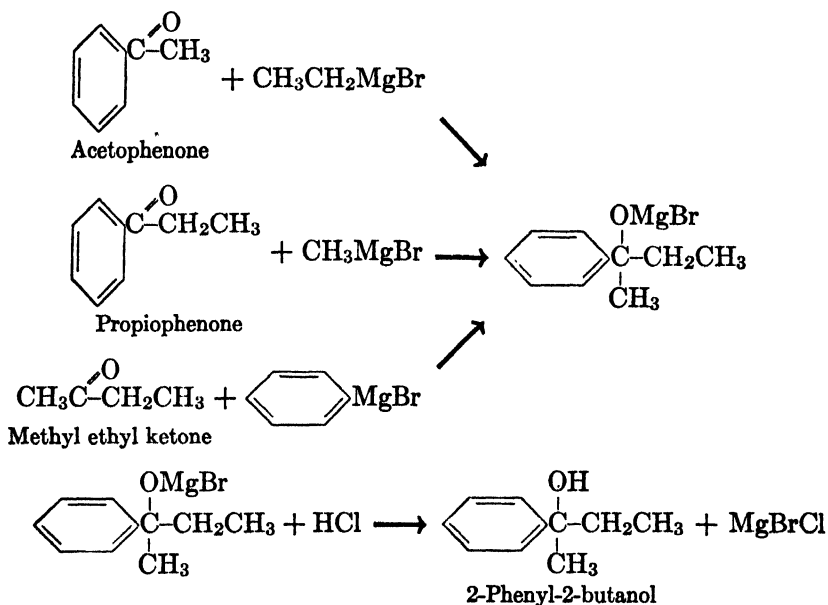
4. *Reaction with the Grignard Reagent.* Addition of the Grignard reagent to the carbonyl group of a ketone leads to the formation of a tertiary alcohol derivative. This is a general method for the preparation of tertiary alcohols. The synthesis of triethylcarbinol from diethyl ketone and ethylmagnesium bromide is an example.



When this synthesis is adapted for the preparation of tertiary alcohols

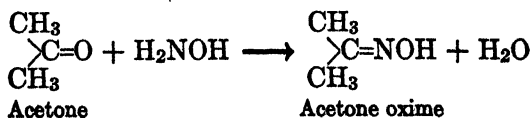
of the type  $\text{R}-\overset{\text{OH}}{\underset{\text{R}'}{\text{C}}}-\text{R}'$ , in which the groups attached to the carbinol

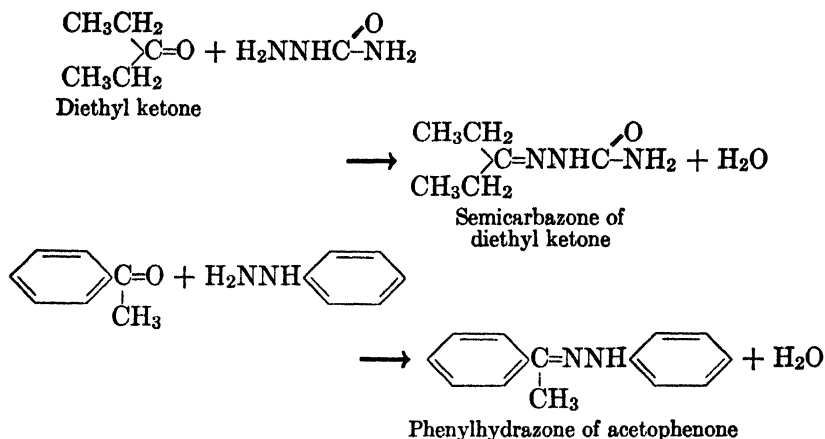
carbon atom are different, three variations are possible. Any one of the R groups may be furnished by the Grignard reagent, the other two being derived from the ketone. The three possibilities are illustrated in the preparation of 2-phenyl-2-butanol.



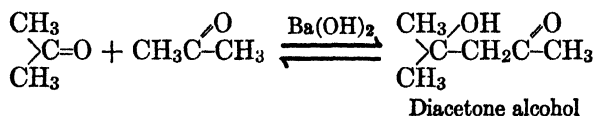
The choice of the pair of reagents to be used is usually made on the basis of their availability. Since propiophenone is the most expensive reagent in the above scheme, either the first or third pair would be selected.

5. *Formation of Oximes, Phenylhydrazones, and Semicarbazones.* Ketones react with hydroxylamine, phenylhydrazine, and semicarbazide in the same manner as do the aldehydes (p. 72). Using acetone, diethyl ketone, and acetophenone as examples we may represent the type reactions as follows:

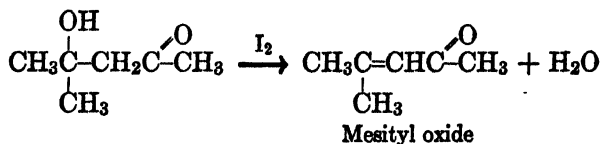




6. *Reactions in the Presence of Alkali.* The simple ketones undergo condensations of the aldol type in the presence of alkali. Diacetone alcohol is obtained from acetone.

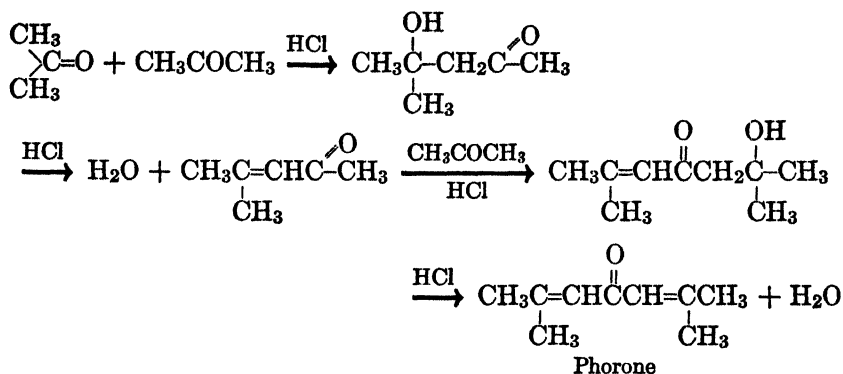


The equilibrium point is far to the left, so that a special method must be used to obtain a good yield of diacetone alcohol. The reaction is run in an extractor, so arranged that the ketone is boiled under reflux and the condensed acetone comes in contact with barium hydroxide as it returns to the boiler. The catalyst causes a small portion of the acetone to change to diacetone alcohol. The liquid which reaches the boiler thus contains a small amount of the addition product and since no alkali is present in the boiler the diacetone alcohol accumulating there does not revert to acetone. The ketone, diacetone alcohol, contains a  $\beta$ -hydroxyl group and an  $\alpha$ -hydrogen atom. Under mild conditions these are eliminated as water, yielding mesityl oxide.

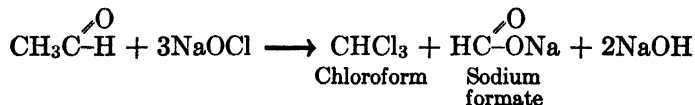


The dehydration can be accomplished by heating diacetone alcohol with iodine or a trace of acid.

Mesityl oxide is also formed from acetone in the presence of strong acid; it reacts with another molecule of acetone to produce phorone.



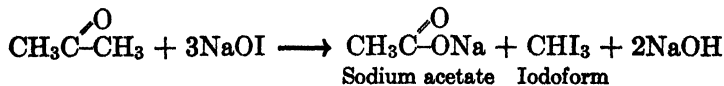
7. *The Haloform Reaction.* One of the characteristic properties of the  $\alpha$ -hydrogen atoms in ketones and aldehydes is the ease of replacement by halogen. Even the salts of hypohalous acids bring about halogenation of aldehydes and ketones which have such hydrogen atoms. The reaction is of particular interest in connection with acetaldehyde and methyl ketones because, in the presence of alkalies, cleavage of the carbon-carbon bond occurs. The products from acetaldehyde and sodium hypochlorite are chloroform and sodium formate.



Bromoform and iodoform are obtained by employing sodium hypobromite and sodium hypoiodite, respectively. When the reaction is used as a test, sodium hypoiodite is employed because the yellow crystals of iodoform can be recognized easily.

The higher aldehydes contain no more than two  $\alpha$ -hydrogen atoms and so cannot yield haloforms upon treatment with hypohalites. Since formaldehyde contains no  $\alpha$ -carbon atom, acetaldehyde is the only aldehyde which gives the haloform reaction.

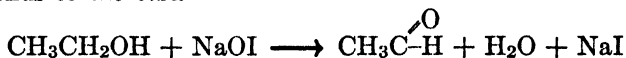
Among the ketones only those having the group  $-\overset{\text{O}}{\text{C}}-\text{CH}_3$  can give haloforms. Thus acetone, methyl ethyl ketone, acetophenone, and other methyl ketones give a positive iodoform test.



As oxidizing agents the hypohalites are capable of attacking primary and secondary alcohols. When ethyl alcohol is treated with sodium hypoiodite it is converted to acetaldehyde and the latter then yields

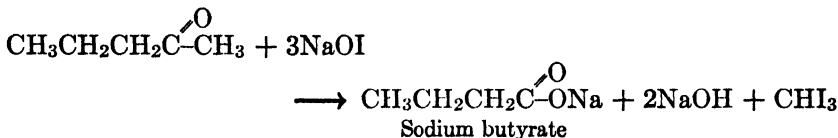
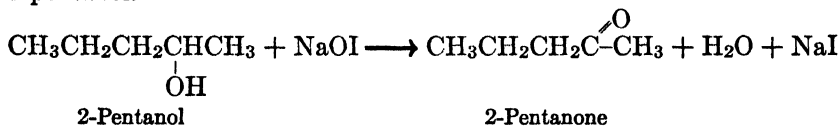


iodoform. Since acetaldehyde is the only aldehyde which gives a positive iodoform test, ethyl alcohol is the only primary alcohol which responds to the test.



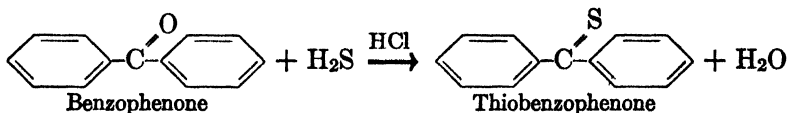
Of the secondary alcohols only those which are methylcarbinols, i.e., which contain the group  $\begin{smallmatrix} \text{CHCH}_3 \\ | \\ \text{OH} \end{smallmatrix}$ , can be oxidized to methyl ketones.

Hence only these can give a positive iodoform test. An example is 2-pentanol.



### Thioaldehydes and Thioketones

The sulfur analogs of the aldehydes are unknown. Attempts to prepare them lead to trimers, similar to paraldehyde (p. 407). The simple ketones also yield trimers when treated with hydrogen sulfide and hydrogen chloride. Monomeric thioketones have been isolated in rare instances (p. 407).



### PROBLEMS

1. Write equations for the reaction of *n*-valeraldehyde with: (a) ammoniacal silver hydroxide, (b) hydrogen in the presence of platinum, (c) an alkali, (d) hydrogen cyanide, (e) sodium bisulfite, (f) sodium bisulfite followed by sodium cyanide, (g) methyl alcohol, (h) methyl alcohol in the presence of mineral acid, (i) *n*-butylmagnesium bromide, (j) hydroxylamine, (k) semicarbazide, (l) phenylhydrazine.

2. Which of the reagents listed above will react with acetone? with diethyl ketone? with cyclohexanone?

3. Write equations for the conversion of *n*-butyl alcohol to: (a) *n*-amyl alcohol, (b) 2-hexanol, (c) di-*n*-butylcarbinol, (d) 2-phenyl-2-hexanol, (e) 3-methyl-3-heptanol.

4. What deductions can be drawn concerning the structure of: (a) a substance which reacts with phenylhydrazine and with Benedict's solution? (b) a substance which reacts with phenylhydrazine but not with Benedict's solution? (c) a substance which does not react with phenylhydrazine but does give a yellow solid when treated with an alkaline solution of iodine?

## SUGGESTED READINGS

WALKER, "Early History of Acetaldehyde and Formaldehyde," *J. Chem. Education* **10**, 546 (1933).

WALKER, "Formaldehyde and Its Polymers," *Ind. Eng. Chem.*, **23**, 1220 (1931).

COOLEY, "Acetone," *Ind. Eng. Chem.*, **29**, 1399 (1937).

## CHAPTER IX

### CARBOXYLIC ACIDS

The carboxyl group,  $\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$ , is capable of dissociating to give hydrogen ions. Hence the compounds containing this group are acids. Those in which the carboxyl group is attached to a paraffin residue are sometimes called fatty acids, since certain of them can be obtained from the natural fats. The names and formulas of some of the straight-chain saturated acids are given in Table XIV. Of those containing more than six carbon atoms, only the ones with even numbers of carbon atoms are common. From the systematic names given it is evident that the ending *oic* is attached to the hydrocarbon stem in naming acids.

TABLE XIV  
SATURATED STRAIGHT-CHAIN ACIDS

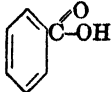
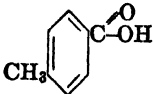
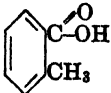
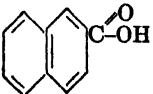
Name	Formula	Melting Point	Boiling Point
Formic acid (methanoic acid)	$\text{HC} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	8.4°	100.7°
Acetic acid (ethanoic acid)	$\text{CH}_3\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	16.6	118.1
Propionic acid (propanoic acid)	$\text{CH}_3\text{CH}_2\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	-22	141.1
Butyric acid (butanoic acid)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	-7.9	163.5
Valeric acid (pentanoic acid)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	-34.5	187
Caproic acid (hexanoic acid)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	-2	205
Caprylic acid (octanoic acid)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	16	237.5
Capric acid (decanoic acid)	$\text{CH}_3(\text{CH}_2)_8\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$	31.5	270

TABLE XIV—Continued  
SATURATED STRAIGHT-CHAIN ACIDS

Lauric acid (dodecanoic acid)	$\text{CH}_3(\text{CH}_2)_{10}\overset{\text{O}}{\parallel}\text{C}-\text{OH}$	44	.....
Myristic acid (tetradecanoic acid)	$\text{CH}_3(\text{CH}_2)_{12}\overset{\text{O}}{\parallel}\text{C}-\text{OH}$	58	.....
Palmitic acid (hexadecanoic acid)	$\text{CH}_3(\text{CH}_2)_{14}\overset{\text{O}}{\parallel}\text{C}-\text{OH}$	64	.....
Stearic acid (octadecanoic acid)	$\text{CH}_3(\text{CH}_2)_{16}\overset{\text{O}}{\parallel}\text{C}-\text{OH}$	69.4	.....

Aromatic acids are named as derivatives of the corresponding hydrocarbons, as shown in Table XV.

TABLE XV  
AROMATIC ACIDS

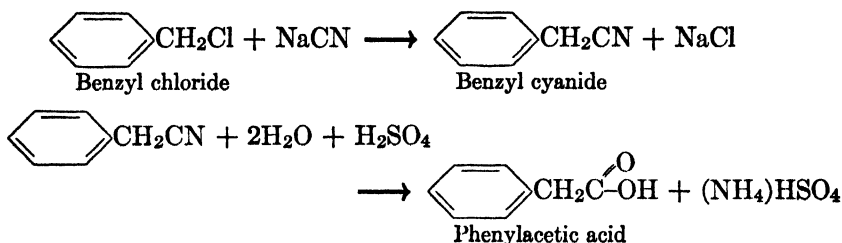
Name	Formula	Melting Point
Benzoic acid		122°
<i>p</i> -Toluic acid		179.6
<i>o</i> -Toluic acid		104
$\beta$ -Naphthoic acid		185

### General Methods of Preparation of Acids

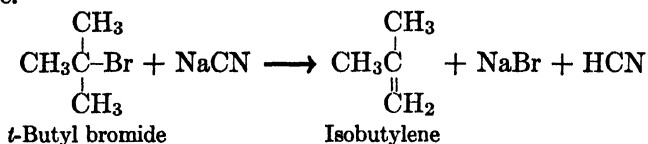
1. **Oxidation of Primary Alcohols and Aldehydes.** It has been mentioned earlier (pp. 65, 68) that acids are obtained by the oxidation of either primary alcohols or aldehydes.

2. **From Alkyl Halides.** An alkyl halide may be converted to an acid of one more carbon atom by either the cyanide synthesis (p. 54) or the Grignard method (pp. 55, 267). If the alkyl halide is primary the

former method is ordinarily used. Thus phenylacetic acid is obtained from benzyl chloride.

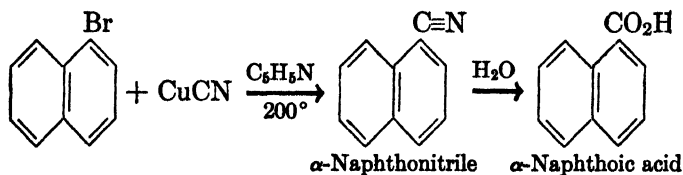


Tertiary alkyl halides undergo dehydrohalogenation (p. 18) under the influence of even very mild alkalis. For this reason the cyanide synthesis fails, and the action of an alkali cyanide on a tertiary halide yields an olefin. The conversion of *t*-butyl bromide to isobutylene is an example.



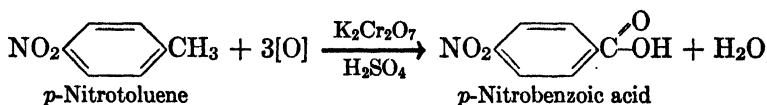
Tertiary halides do yield Grignard reagents, however, and thus can be converted to acids. *t*-Butyl chloride can be converted to trimethylacetic acid by this method (p. 55). The Grignard method can also be employed with secondary halides, for which the cyanide method is rarely useful.

Aryl halides are inert to aqueous solutions of alkali cyanides. However, they do react with anhydrous cuprous cyanide in the presence of an organic base such as pyridine ( $\text{C}_5\text{H}_5\text{N}$ , p. 252).  $\alpha$ -Naphthoic acid may be prepared from  $\alpha$ -bromonaphthalene by this method.



Aryl bromides and iodides can be converted to Grignard reagents, so the Grignard synthesis (p. 267) is useful in the preparation of aromatic acids.

**3. Oxidation of Side Chains.** Aromatic acids often are obtained conveniently by the oxidation of compounds containing side chains (p. 40). Thus *p*-nitrobenzoic acid is prepared from *p*-nitrotoluene.



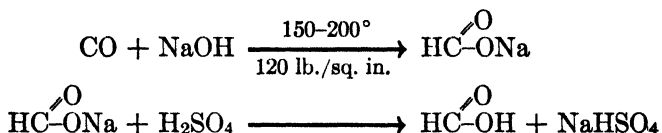
The *p*-nitrotoluene is made by the nitration of toluene (p. 39).

A number of other methods for the synthesis of acids are available. These are discussed in later sections.

### Properties of the Simple Acids

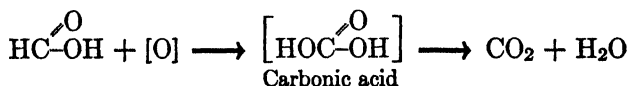
Formic acid is a colorless liquid with a sharp, pungent odor. It is very irritating to the skin; the unpleasant effect of the stings of many insects is due to formic acid. As the name implies (*formica*, ant), the acid was first obtained from ants.

Sodium formate is prepared commercially by heating sodium hydroxide with carbon monoxide under pressure. Anhydrous formic acid is obtained from the dry sodium salt by action of concentrated sulfuric acid.

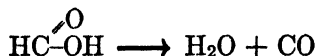


Formic acid is employed in the textile, leather, and rubber industries. Since it is a relatively weak acid it can be applied safely to products, such as those indicated, which are damaged by treatment with mineral acids.

Formic acid differs from all other organic acids in having a hydrogen atom rather than an organic radical attached to the carboxyl group. It may be regarded as being at once an aldehyde and an acid. This view is in harmony with its action as a reducing agent (p. 392).



When a mixture of formic and sulfuric acids is heated the formic acid decomposes to water and carbon monoxide.



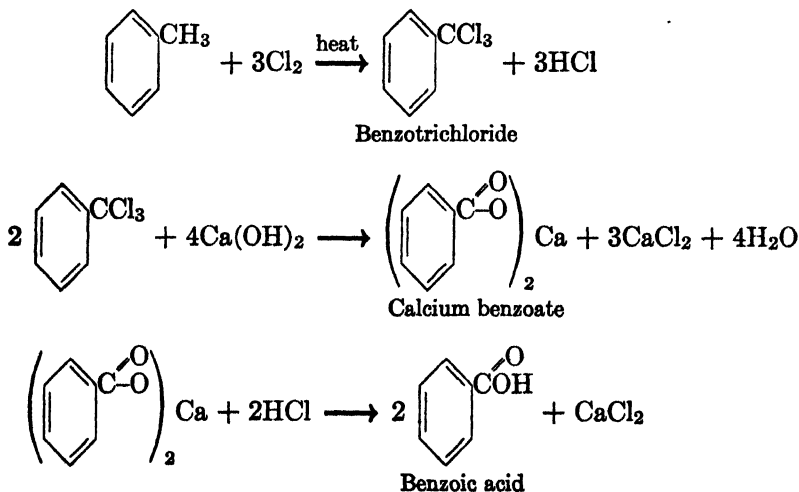
Acetic acid is the most important of the simple acids. As indicated above (p. 23) it is prepared by the oxidation of acetaldehyde. Since acetaldehyde may be obtained either from ethyl alcohol or from acetylene, the raw material for the commercial preparation of acetic acid may be sugar, coke, or petroleum. The acid is a liquid boiling at 118.1°

It freezes at a point just below room temperature ( $16.6^{\circ}$ ); hence the name glacial acetic acid is applied to the pure substance.

Acetic acid is widely used in industrial processes where a weak acid is desired. It is most valuable as a raw material for the preparation of cellulose acetate (p. 201).

Vinegar is essentially a dilute solution of acetic acid. It is obtained by the oxidation of dilute ethyl alcohol (fermented apple cider) by the oxygen of the air in the presence of "mother of vinegar" (*bacterium aceti*).

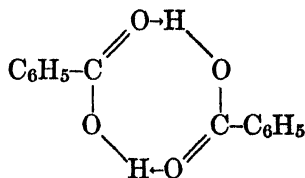
Benzoic acid, the simplest of the aromatic acids, is a white crystalline solid. It is prepared commercially by several different methods. In one of them, phthalic acid (p. 134) is used as the raw material. In another process toluene is oxidized to benzoic acid and water. An interesting commercial preparation involves the chlorination of toluene. The chlorine substitutes only in the side chain if the reaction is carried out under appropriate conditions (p. 40). The product, benzotrichloride, in which the side chain is completely chlorinated, can be hydrolyzed to benzoic acid.



Benzoic acid, as its sodium salt, is extensively used as a preservative for foods and fruit juices.

Consideration of the boiling points of the acids reveals that they are less volatile than other substances of similar molecular weights. This leads to the supposition that the acids are associated. Indeed, measurement of the molecular weight of benzoic acid dissolved in a hydrocarbon solvent shows it to have the *dimeric* formula  $(\text{C}_6\text{H}_5\text{CO}_2\text{H})_2$ . The forma-

tion of a dimer can be explained on the basis of a cyclic structure involving hydrogen bonds, as shown below.



Dimer of benzoic acid

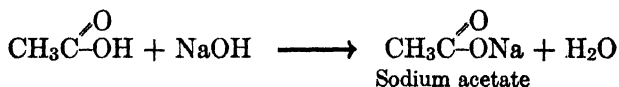
Rings of this type, formed by a coordination process, are known as *chelate rings* ( $\chi\eta\lambda\eta$ , a crab's claw) (p. 210). Other carboxylic acids likewise exist as chelate dimers.

### DERIVATIVES OF THE ACIDS

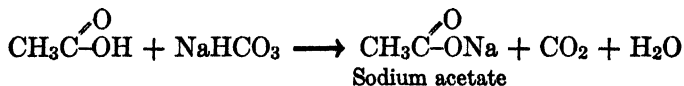
A molecule containing the carboxyl group undergoes reactions to form several types of compounds. The most important of these are the salts, esters, acyl halides, acid anhydrides, and amides.

#### Salts

The carboxylic acids react with alkalis to form salts. Sodium acetate is obtained from acetic acid and sodium hydroxide.



Since the carboxylic acids are stronger than carbonic acid, carbonates or bicarbonates may be used instead of hydroxides. Thus sodium acetate may also be prepared from acetic acid and sodium bicarbonate.



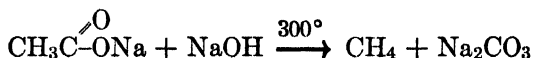
The alkali salts of organic acids resemble inorganic salts in many ways. They are soluble in water and insoluble in organic solvents such as ether and carbon tetrachloride. They are ionic substances, as is shown by the electrical conductivity of their solutions in water. Since they are salts of strong bases with relatively weak acids, their water solutions are slightly alkaline.

The organic acids can be recovered from their salts by treatment of the latter with mineral acids. The conversion of calcium benzoate to



benzoic acid by treatment with hydrochloric acid, mentioned above, is an example.

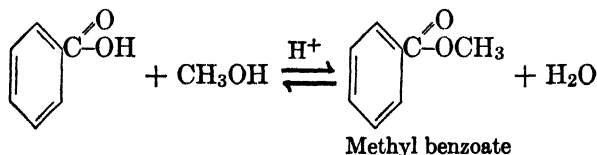
When the sodium salt of an acid is heated with sodium hydroxide it decomposes to a hydrocarbon and sodium carbonate. Methane is obtained from sodium acetate.



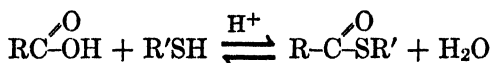
Since this reaction involves the removal of the carboxyl group from an acid derivative, it may be considered as an indirect *decarboxylation* of the acid ( $\text{RCO}_2\text{H} \longrightarrow \text{RH}$ ). It is sometimes employed as a method for the preparation of hydrocarbons.

### Esters

The reaction of alcohols with oxygen acids to give esters has been mentioned earlier (p. 51). The most important esters are derived from the carboxylic acids. They are often made by the direct esterification of the acid by treatment with the alcohol in the presence of a trace of mineral acid. The latter acts as a catalyst. The reaction of esterification is reversible, so in order to obtain good yields it is desirable to use an excess of one of the reactants. The preparation of methyl benzoate from methyl alcohol and benzoic acid illustrates the reaction.



If a mercaptan is allowed to react with an acid a thio ester is obtained. The reaction is of particular interest because it proceeds by elimination of water rather than of hydrogen sulfide.

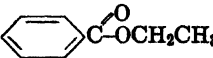
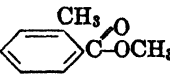
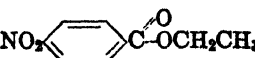


This suggests that esterification involves the loss of the *hydrogen atom* of the alcohol and the *hydroxyl group* of the acid. On the basis of the alternate scheme of elimination of the hydrogen atom of the acid and the hydroxyl group of the alcohol, the reaction of the mercaptans would be expected to produce normal esters and hydrogen sulfide.

An ester is named with reference to the alcohol and acid from which it is derived. A number of examples are given in Table XVI, which also shows the boiling points of some of the common esters. A com-

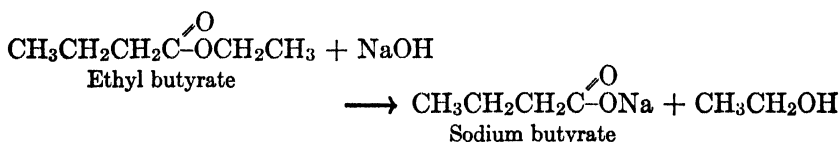
parison of the boiling points of the lower esters with those of the acids and alcohols is interesting. For example, methyl formate ( $\text{HCO}_2\text{CH}_3$ , b.p.  $31.5^\circ$ ) is more volatile than either the acid ( $\text{HCO}_2\text{H}$ , b.p.  $100.7^\circ$ ) or the alcohol ( $\text{CH}_3\text{OH}$ , b.p.  $65^\circ$ ) from which it is derived, although the ester has a higher molecular weight than either of its progenitors.

TABLE XVI  
SOME SIMPLE ESTERS

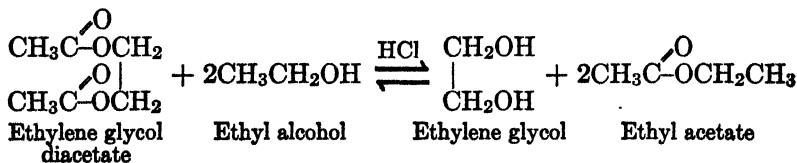
Name	Formula	Boiling Point
Methyl formate	$\text{HC}-\overset{\text{O}}{\parallel}\text{OCH}_3$	$31.5^\circ$
Ethyl formate	$\text{HC}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_3$	$54.3$
Methyl acetate	$\text{CH}_3\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_3$	$57.1$
Ethyl acetate	$\text{CH}_3\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_3$	$77.1$
Isopropyl acetate	$\text{CH}_3\text{C}-\overset{\text{O}}{\parallel}\text{OCHCH}_3$ $\quad\quad\quad\text{CH}_3$	$89$
<i>n</i> -Butyl acetate	$\text{CH}_3\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	$126.5$
<i>n</i> -Amyl acetate	$\text{CH}_3\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	$148$
Methyl propionate	$\text{CH}_3\text{CH}_2\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_3$	$79.9$
<i>n</i> -Propyl propionate	$\text{CH}_3\text{CH}_2\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_2\text{CH}_3$	$123.3$
Ethyl butyrate	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_3$	$121.3$
Ethyl isobutyrate	$\text{CH}_3\text{CH}(\text{CH}_3)\text{C}-\overset{\text{O}}{\parallel}\text{OCH}_2\text{CH}_3$	$111.7$
Ethyl benzoate		$212.6$
Methyl <i>o</i> -toluate		$213$
Ethyl <i>p</i> -nitrobenzoate		(m.p. $57^\circ$ )

The ester has no active hydrogen atom capable of forming a hydrogen bond and thus, unlike the acid (p. 88) and alcohol (p. 43) it is a "normal" or unassociated liquid.

**Hydrolysis and Saponification of Esters.** As indicated by the reversibility of the esterification reaction, an ester may be hydrolyzed to regenerate the alcohol and acid. Usually it is more convenient to carry out the hydrolysis in the presence of alkali, so that the organic acid is neutralized as rapidly as it is formed. Since the acid so removed is one of the components of the equilibrium mixture (acid, alcohol, ester, and water), the reaction becomes irreversible and quantitative. Another advantage is that the reaction can be carried out in an alcohol solution containing only a little water. Many esters are nearly insoluble in water and hence are hydrolyzed by water and a trace of acid only very slowly. Addition of an alcohol as a solvent would, of course, repress hydrolysis or bring about the formation of a new ester, if the solvent alcohol were different from that involved in the ester. If alkali is added to the alcohol solution the acid is removed, as the sodium salt, as rapidly as it is formed and the ester is hydrolyzed quantitatively. The alkaline hydrolysis of esters is known as *saponification*. The term arose from the fact that soaps are made by the alkaline hydrolysis of certain esters (p. 107). The saponification of ethyl butyrate illustrates the reaction.

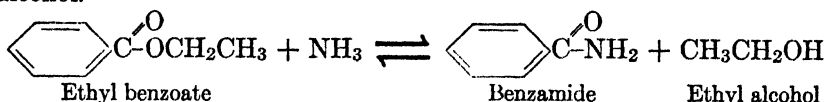


**Transesterification (Ester Interchange).** Under appropriate conditions an ester of one alcohol reacts with a second alcohol to form a new ester. The alcohol concerned in the original ester is liberated. Because the process is reversible it is necessary to employ a large excess of the reacting alcohol to obtain good yields. The reaction of ethylene glycol diacetate with ethyl alcohol is an example.

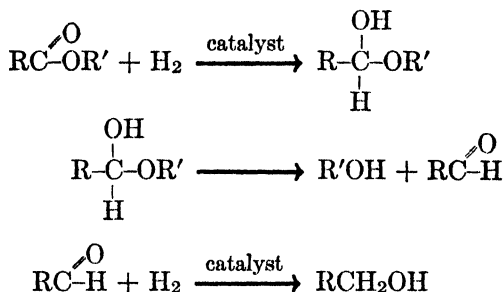


As indicated in the equation, a trace of mineral acid may be used as a catalyst. Strangely enough, an alkaline catalyst also may be used; sodium methoxide ( $\text{NaOCH}_3$ ) is often employed. The reaction is most useful in connection with the natural fats (p. 109).

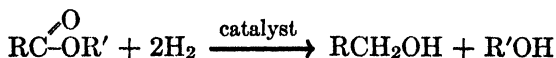
**Ammonolysis of Esters.** The reactions of esters described above may be considered as examples of hydrolysis and alcoholysis, respectively. The reaction of an ester with ammonia follows a similar course and may be referred to as an ammonolysis. The products are an *amide* and an alcohol. Ethyl benzoate and ammonia yield benzamide and ethyl alcohol.



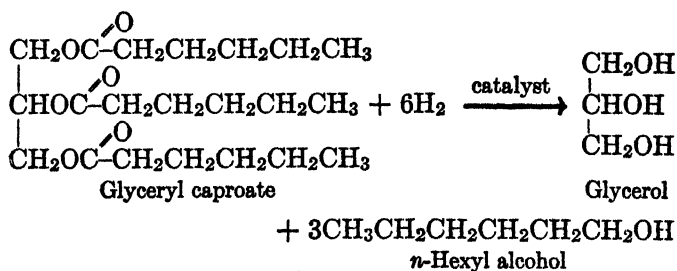
**Hydrogenation of Esters.** The carbonyl group of the ester linkage is capable of undergoing catalytic reduction under vigorous conditions. It is possible that the first step is addition of hydrogen to the carbon-oxygen double bond, yielding a hemiacetal; the latter dissociates to the alcohol and the aldehyde, and the aldehyde is further reduced to a primary alcohol. These steps may be represented as follows:



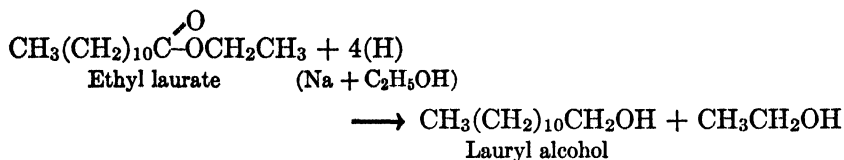
The sum of these reactions may be represented by the following equation:



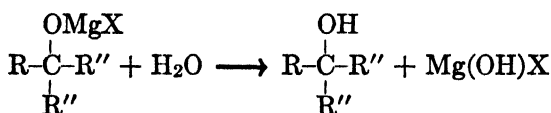
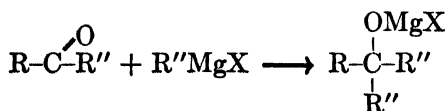
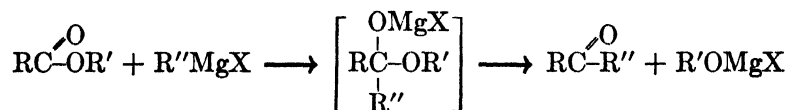
The hydrogenation of glyceryl caproate is an example of this reaction. The catalyst ordinarily used is copper chromite. The reaction is carried out at temperatures above 200° and at pressures in the neighborhood of 3000 lb. per square inch.



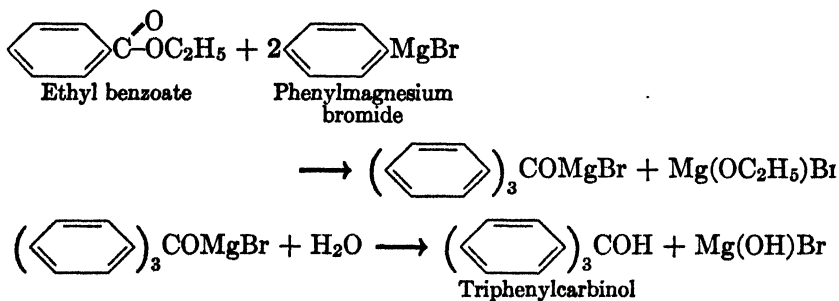
The reduction also can be effected by means of metallic sodium and alcohol. For example, lauryl alcohol was formerly prepared by this method.



**Reaction of Esters with the Grignard Reagent. Synthesis of Tertiary Alcohols.** The addition products formed from esters and Grignard reagents are unstable. They combine with more of the Grignard reagent, either directly or after decomposing to ketones, to produce derivatives of tertiary alcohols. The various steps in the synthesis of tertiary alcohols by this method may be represented as follows:



Tertiary alcohols in which the three groups attached to the carbinol carbon atom are alike can be prepared by proper selection of the reagents. For example, triphenylcarbinol is obtained from ethyl benzoate and phenylmagnesium bromide.



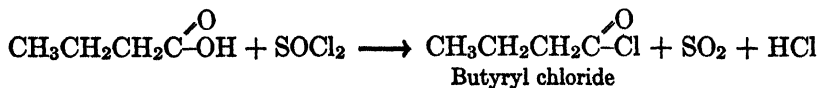
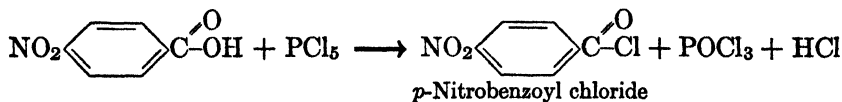
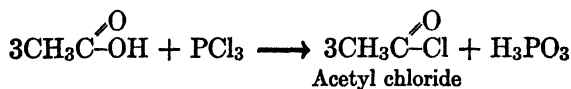
### The Acyl Halides

When acids are brought into contact with certain halides and oxyhalides of phosphorus and sulfur, the hydroxyl group of the acid is replaced by a halogen atom. The acyl bromides and iodides are of little importance but the chlorides are used extensively. The names, formulas, and boiling points of a few acyl chlorides are given in Table XVII.

TABLE XVII  
ACYL CHLORIDES

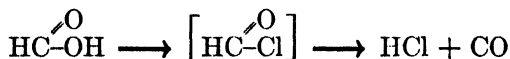
Name	Formula	Boiling Point
Acetyl chloride	$\text{CH}_3\text{C}(=\text{O})\text{Cl}$	52°
Propionyl chloride	$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{Cl}$	80
Butyryl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{Cl}$	102
Isobutyryl chloride	$\text{CH}_3\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{Cl}$	92
Valeryl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{Cl}$	128
Benzoyl chloride	$\text{C}_6\text{H}_5\text{C}(=\text{O})\text{Cl}$	197
<i>p</i> -Bromobenzoyl chloride	$\text{BrC}_6\text{H}_4\text{C}(=\text{O})\text{Cl}$	247 (m.p. 42°)

The reagents most often employed for the preparation of acyl chlorides are phosphorus trichloride ( $\text{PCl}_3$ ), phosphorus pentachloride ( $\text{PCl}_5$ ), and thionyl chloride ( $\text{SOCl}_2$ ). Equations showing the products obtained from each of these reagents are given below.



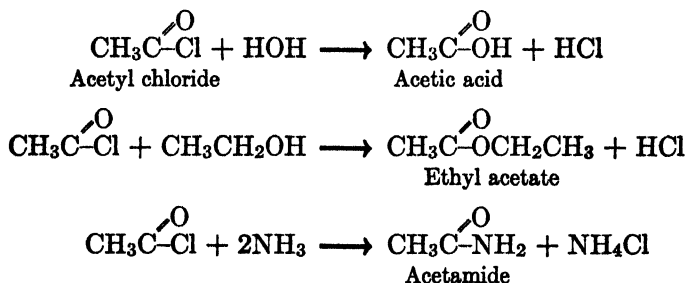
Whenever it can be used, thionyl chloride is a superior reagent for the preparation of acyl chlorides because the by-products are gases. If the chloride being prepared boils somewhat higher than thionyl chloride (b.p. 78.8°), it can often be obtained sufficiently pure simply by treating the acid with a slight excess of thionyl chloride and heating the reaction mixture on the steam bath to remove the excess reagent.

The chloride of formic acid is unknown. All attempts to prepare it have led to the formation of carbon monoxide and hydrogen chloride.



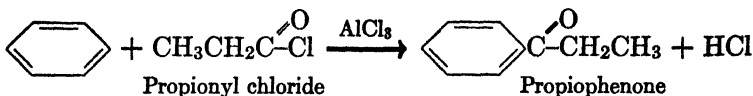
There is evidence that the decomposition of formyl chloride is reversible, since with certain reagents a mixture of hydrogen chloride and carbon monoxide gives products which may be considered as derivatives of formic acid (p. 289). The instability of formyl chloride recalls the decomposition of formic acid in the presence of dehydrating agents (p. 87).

**Reactions of Acyl Chlorides.** The acyl chlorides react with many compounds containing the groups -OH and -N-H. Thus they react with water, alcohols, and ammonia, to give acids, esters, and amides, respectively. In each case hydrogen chloride is formed simultaneously; if ammonia is one of the reactants the hydrogen chloride is converted to ammonium chloride. The reactions are illustrated with acetyl chloride.

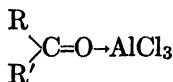


All these reactions take place very rapidly and with the evolution of heat. The acyl chlorides are thus convenient reagents for the introduction of acyl groups by reaction with compounds which have hydroxyl or amino groups.

**The Friedel-Crafts Synthesis of Ketones.** Acyl chlorides react with aromatic hydrocarbons in the presence of aluminum chloride to give ketones. For example, propiophenone is obtained from propionyl chloride, benzene, and aluminum chloride.



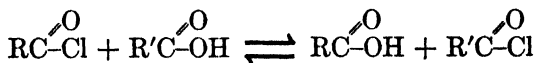
In the preparation of ketones by this method the catalyst, aluminum chloride, must be present in an amount equivalent to the quantity of acyl chloride used, because the ketone and the aluminum chloride form a coordination compound. It is believed to have the following structure.



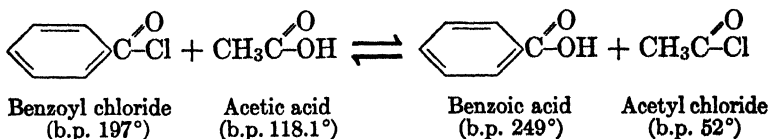
Coordination compound from a ketone  
and aluminum chloride

When the reaction mixture is treated with water the coordination complex is destroyed and the ketone is obtained.

**Reaction of Acyl Chlorides with Acids.** When an acyl chloride is mixed with a carboxylic acid, an equilibrium of the following type is established.



The reaction is the basis of an excellent method for the preparation of certain acyl chlorides. For example, one of the most convenient laboratory preparations of acetyl chloride utilizes benzoyl chloride and acetic acid as the starting materials.



Since acetyl chloride is the lowest-boiling component of the equilibrium mixture it can be removed by heating the reaction mixture under a fractionating column. Removal of the product in this way forces the reaction to the right, with the result that the yield is very satisfactory.

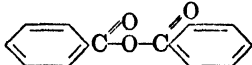
### The Acid Anhydrides

Acid anhydrides have the general formula  $\text{RC}(=\text{O})\text{O}\text{C}(=\text{O})\text{R}'$ . In the most common anhydrides the groups R and R' are identical. These are known as *simple* anhydrides, in contrast to the *mixed* anhydrides in which the groups are different. The simple anhydrides are named with reference to the corresponding acids, as may be seen by examination of Table XVIII.

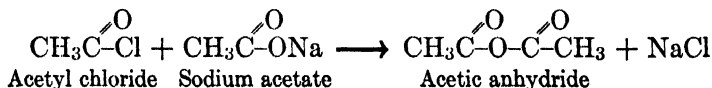


TABLE XVIII

## SIMPLE ACID ANHYDRIDES

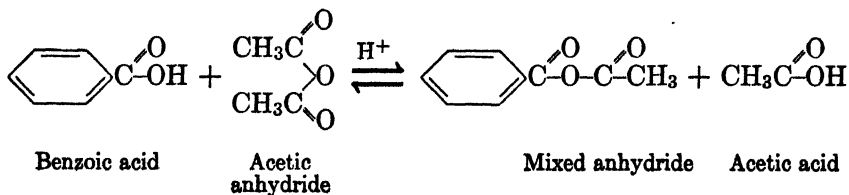
Name	Formula	Boiling Point
Acetic anhydride	$\text{CH}_3\text{C}(=\text{O})\text{O}\text{C}(=\text{O})\text{CH}_3$	140°
Propionic anhydride	$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{O}\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	169.3
Butyric anhydride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{O}\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$	198
Isobutyric anhydride	$\text{CH}_3\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{O}\text{C}(=\text{O})\text{CH}(\text{CH}_3)\text{CH}_3$	182.5
Valeric anhydride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{O}\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	215
Benzoic anhydride		360 (m.p. 42°)

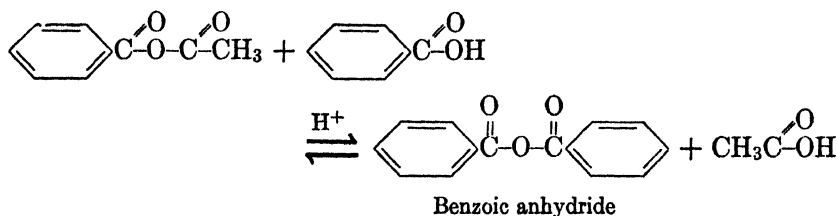
Acid anhydrides are sometimes prepared in the laboratory by the interaction of an acyl chloride and a salt. For example, acetic anhydride may be obtained from acetyl chloride and sodium acetate.



If the chloride and the salt employed are derived from different acids, a mixed anhydride is obtained.

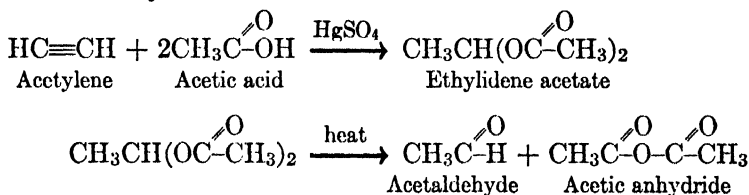
Anhydrides are also obtained by a process of interchange similar to that sometimes employed in the preparation of acyl chlorides (p. 97). One acid is treated with the anhydride of a second acid, yielding a mixture containing both acids, both simple anhydrides, and the mixed anhydride. The reaction is illustrated by the products obtained when acetic anhydride and benzoic acid are heated with a trace of phosphoric acid.





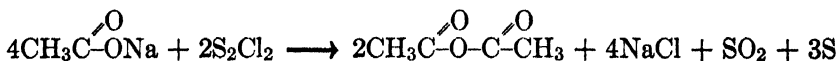
By heating the mixture under a fractionating column the acetic acid can be removed, thereby driving the reaction to the right.

The most important anhydride in industrial chemistry is acetic anhydride. It is obtained commercially from acetylene by an interesting sequence of reactions. Part of the acetylene is converted to acetic acid by hydration and oxidation (p. 23). Acetic acid and acetylene are then combined, in the presence of mercuric sulfate, to form ethylidene acetate. When the latter is heated it decomposes to acetic anhydride and acetaldehyde.

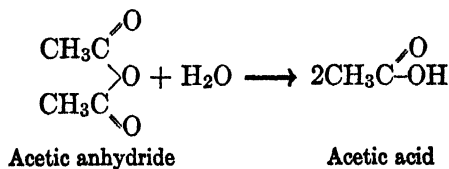


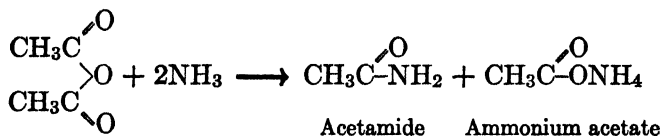
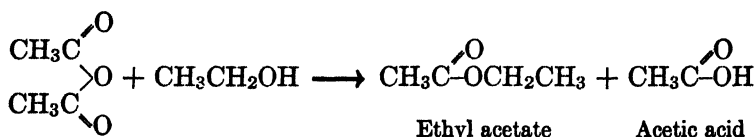
The acetaldehyde is converted to acetic acid, which is used in the first step of the process.

An older industrial process utilizes the reaction between acetic acid or its salts and sulfur chloride.



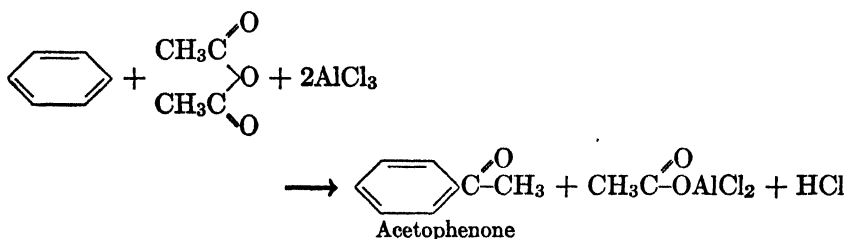
**Reactions of Acid Anhydrides.** The acid anhydrides closely resemble the acyl chlorides in their chemical behavior. Thus, they react with water, alcohol, and ammonia to give acids, esters, and amides, respectively. The equations for the reactions of acetic anhydride with these substances are given below.





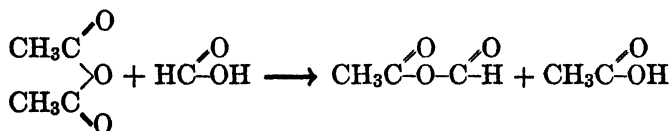
It is to be noted that these reactions are exactly parallel to those of acetyl chloride with the same reagents. The acyl chlorides may, in fact, be considered as mixed anhydrides derived from carboxylic acids and hydrochloric acid.

Acid anhydrides also react with aromatic hydrocarbons under the conditions of the Friedel-Crafts reaction. Thus, acetophenone is made from acetic anhydride, benzene, and aluminum chloride.

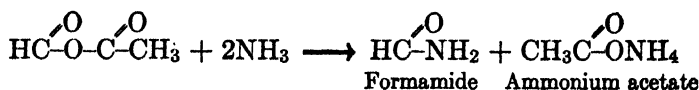


The reaction of an anhydride requires twice as much aluminum chloride as does that of an acyl chloride. One molecule forms a coordination compound with the ketone (p. 97) and another reacts with the organic acid to form a mixed salt.

It is of interest to note that formic anhydride, like formyl chloride, is unstable and has not been prepared. A mixed anhydride derived from acetic and formic acids can be obtained from acetic anhydride and formic acid.



The mixed anhydride reacts with compounds containing active hydrogen atoms to introduce the formyl group. Thus it yields formamide when treated with ammonia.



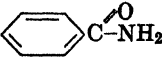
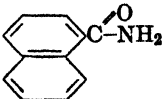
The mixed anhydride is unstable at its boiling point at ordinary pressure, but for most purposes it is unnecessary to isolate it. One simply uses a mixture of acetic anhydride and formic acid.

### The Amides

The amides ( $\text{RC}-\overset{\text{O}}{\text{NH}_2}$ ) may be regarded as acyl derivatives of ammonia. From the consideration that the acyl derivatives ( $\text{RC}-\overset{\text{O}}{\text{OH}}$ ) of the neutral substance, water, are acids it would be predicted that the amides are more acid (less basic) than ammonia. It happens that the acidifying influence of the acyl groups just neutralizes the basic properties of ammonia, for the amides are neutral substances.

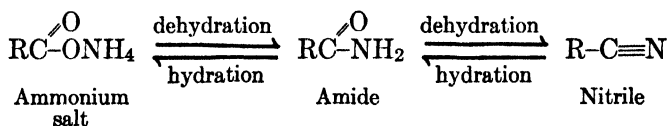
TABLE XIX

## AMIDES

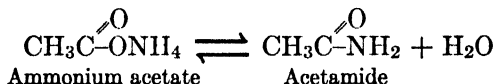
Name	Formula	Melting Point	Boiling Point
Formamide	$\text{HC}-\overset{\text{O}}{\text{NH}_2}$	2.5°	195°
Acetamide	$\text{CH}_3\text{C}-\overset{\text{O}}{\text{NH}_2}$	81	222
Propionamide	$\text{CH}_3\text{CH}_2\text{C}-\overset{\text{O}}{\text{NH}_2}$	79	213
Butyramide	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}-\overset{\text{O}}{\text{NH}_2}$	116	216
Valeramide	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}-\overset{\text{O}}{\text{NH}_2}$	106	...
Benzamide		130	...
$\alpha$ -Naphthamide		202	...

Of the simple amides, all but formamide are solids. The names, formulas, melting points, and boiling points, of some of them are given in Table XIX.

The formation of amides from esters (p. 93), acyl chlorides (p. 96), and anhydrides (p. 99) has been mentioned. All these reactions are used in the laboratory as preparative methods. Amides are also obtained by dehydration of ammonium salts and by hydration of nitriles. The relationship between ammonium salts, amides, and nitriles is shown by the following equation.



The dehydration of ammonium salts to amides is often effected by heating. For example, acetamide is made conveniently by heating ammonium acetate.



### Naturally Occurring Esters

Most of the volatile esters have pleasant odors and many of them occur in fruits and flowers. Synthetic perfumes and flavors are often mixtures of esters. Butyl acetate and isoamyl acetate have the odor of bananas. Amyl acetate is reminiscent of pears. Amyl undecanoate

$[\text{CH}_3(\text{CH}_2)_9\overset{\text{O}}{\parallel}\text{C}-\text{OCH}_2(\text{CH}_2)_3\text{CH}_3]$  has a roselike odor.

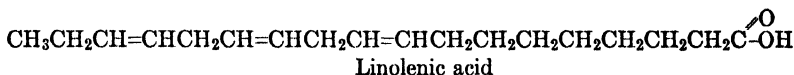
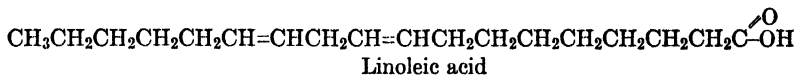
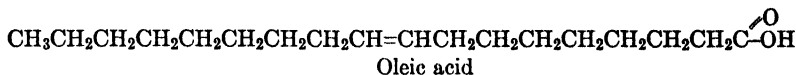
The most important of the natural esters are those which make up the animal and vegetable fats. These will now be considered.

### Fats

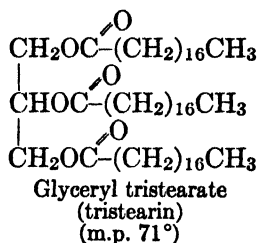
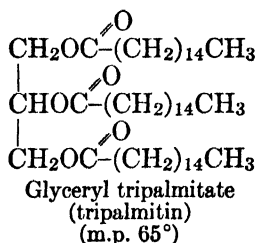
The animal and vegetable fats and oils are glyceryl esters of organic acids. Hydrolysis converts them to glycerol and mixtures of saturated and unsaturated acids. It is a striking fact that the acids obtained are, with very few exceptions, *straight-chain acids containing even numbers of carbon atoms*. The saturated members most frequently

encountered are lauric acid  $[\text{CH}_3(\text{CH}_2)_{10}\overset{\text{O}}{\parallel}\text{C}-\text{OH}]$ , myristic acid  $[\text{CH}_3(\text{CH}_2)_{12}\overset{\text{O}}{\parallel}\text{C}-\text{OH}]$ , palmitic acid  $[\text{CH}_3(\text{CH}_2)_{14}\overset{\text{O}}{\parallel}\text{C}-\text{OH}]$ , and stearic acid  $[\text{CH}_3(\text{CH}_2)_{16}\overset{\text{O}}{\parallel}\text{C}-\text{OH}]$ . The most common unsaturated acids

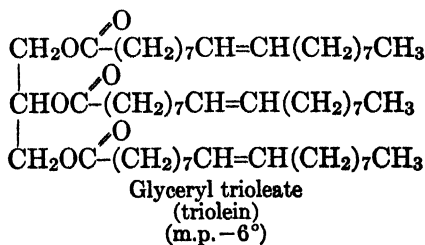
have the carbon skeleton of stearic acid. Oleic acid ( $C_{17}H_{33}CO_2H$ ) has eighteen carbon atoms with one double bond at the central point of the chain; linoleic acid ( $C_{17}H_{31}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-OH$ ) has eighteen carbons with two double bonds; and linolenic acid ( $C_{17}H_{29}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-OH$ ) has eighteen carbons with three double bonds. The ethylenic linkages in linoleic and linolenic acids are not conjugated.



Examination of the acids produced by the hydrolysis of a typical solid fat, such as beef tallow, reveals that the substance is composed largely of the glyceryl esters of the saturated acids, palmitic and stearic acids. The glyceryl esters are known as tripalmitin and tristearin, respectively; both melt well above room temperature.

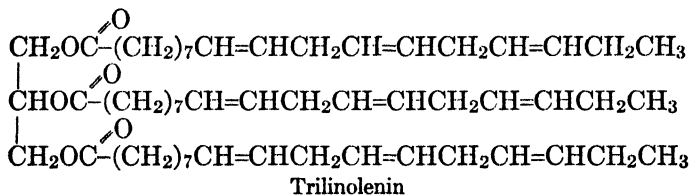
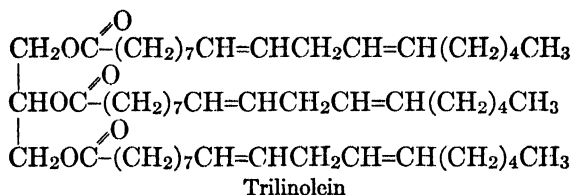


The acid obtained in largest quantity from olive oil is oleic acid. The chief constituent of this oil must therefore be glyceryl trioleate or triolein; this substance is a liquid at ordinary temperatures.

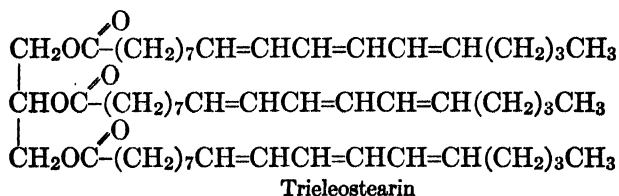


This comparison illustrates the essential difference in the composition of solid and liquid fats. The solid fats contain a higher proportion of saturated glyceryl esters than do the liquid fats (oils).

*Drying oils* such as linseed oil and tung oil are those which change to tough solids on exposure to the air. They invariably contain a large proportion of esters of the highly unsaturated acids. For example, linseed oil contains considerable quantities of trilinolein and trilinolenin.



Tung oil consists largely of trieleostearin. Eleostearic acid is an isomer of linolenic acid; in it the three double bonds are conjugated.



It has been mentioned that the most common fatty acids contain sixteen and eighteen carbon atoms. Esters of lower acids do occur, however. The mixture of acids obtained by hydrolysis of nutmeg oil contains a substantial proportion of myristic acid. Butter contains glyceryl esters of all the even carbon saturated acids from butyric to stearic acids. In Table XX is given the composition of the mixture of acids obtained by hydrolysis of a sample of butter. The consistency of butter is due partly to the presence of the unsaturated component and partly to the presence of esters of the lower acids.

Coconut oil is essentially saturated. Its consistency is approximately that of butter, but it is called an oil because it is a liquid in the warm

regions where it is produced. The low melting point of this substance is to be ascribed largely to the presence of esters of lower acids. The composition of the acid mixture from coconut oil is given in Table XXI. It is of interest to note that lauric acid is the chief component.

TABLE XX

## COMPOSITION OF MIXTURE OF ACIDS FROM HYDROLYSIS OF BUTTER

Fatty Acid	Formula	Per Cent in Mixture
Butyric	$\text{CH}_3(\text{CH}_2)_2\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	3.2
Caproic	$\text{CH}_3(\text{CH}_2)_4\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	1.4
Caprylic	$\text{CH}_3(\text{CH}_2)_6\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	1.8
Capric	$\text{CH}_3(\text{CH}_2)_8\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	1.8
Lauric	$\text{CH}_3(\text{CH}_2)_{10}\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	6.9
Myristic	$\text{CH}_3(\text{CH}_2)_{12}\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	22.6
Palmitic	$\text{CH}_3(\text{CH}_2)_{14}\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	22.6
Stearic	$\text{CH}_3(\text{CH}_2)_{16}\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	11.4
Oleic	$\text{C}_{17}\text{H}_{33}\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{C} \end{smallmatrix}\text{-OH}$	27.4
		<hr/> 99.1

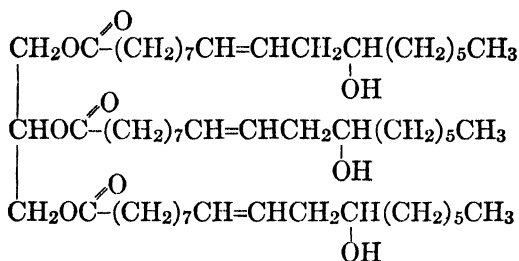
TABLE XXI

## COMPOSITION OF MIXTURE OF ACIDS FROM HYDROLYSIS OF COCONUT OIL

Fatty Acid	Formula	Per Cent in Mixture
Caproic	$\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$	0.2
Caprylic	$\text{CH}_3(\text{CH}_2)_6\text{CO}_2\text{H}$	8.0
Capric	$\text{CH}_3(\text{CH}_2)_8\text{CO}_2\text{H}$	7.0
Lauric	$\text{CH}_3(\text{CH}_2)_{10}\text{CO}_2\text{H}$	48.0
Myristic	$\text{CH}_3(\text{CH}_2)_{12}\text{CO}_2\text{H}$	17.5
Palmitic	$\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$	8.8
Stearic	$\text{CH}_3(\text{CH}_2)_{16}\text{CO}_2\text{H}$	2.0
Oleic	$\text{C}_{17}\text{H}_{33}\text{CO}_2\text{H}$	6.0
Linoleic	$\text{C}_{17}\text{H}_{31}\text{CO}_2\text{H}$	2.5
		<hr/> 100.0

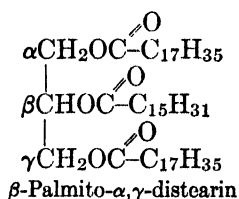
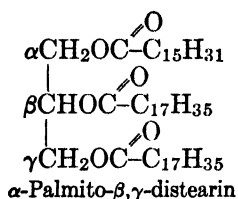


Castor oil is unique in that it consists of the glyceryl ester of a hydroxy acid. It is largely glyceryl triricinoleate. Ricinoleic acid may be considered as a hydroxyoleic acid.

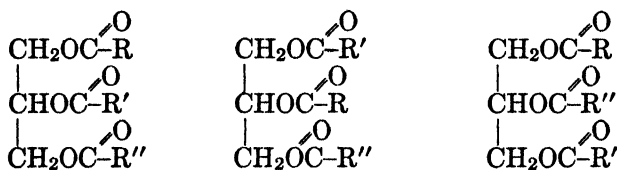


Triricinolein

Compounds such as triolein and tristearin are considered as *simple* glyceryl esters, that is, the three acid radicals in such an ester are identical. The naturally occurring fats and oils also contain *mixed* glyceryl esters, in which two or three different acid radicals are present in the molecules. An ester of one molecule of glycerol, two molecules of stearic acid, and one molecule of palmitic acid, called palmitodistearin, occurs in beef tallow. Two formulas for such an ester are possible, as shown below.



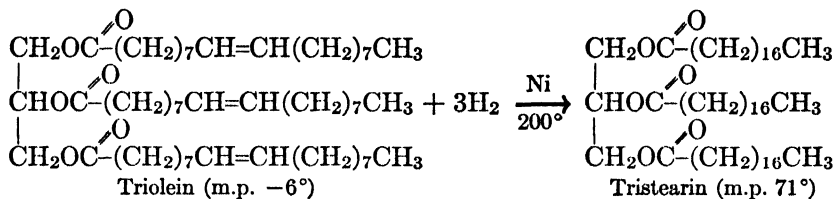
Mixed glyceryl esters derived from three different fatty acids may exist in three isomeric forms. The general formulas for such isomers are given below.



Isomeric mixed glyceryl esters

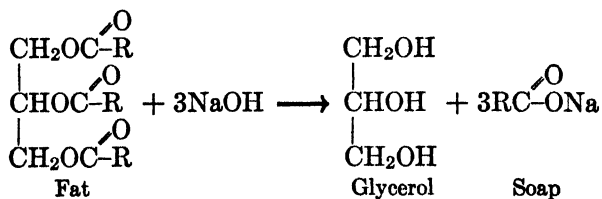
Because of the existence of isomeric mixed esters the natural fats contain many more components than is indicated by the analysis of the mixture of acids obtained by hydrolysis.

**The Hardening of Vegetable Oils.** Vegetable oils such as cottonseed oil and soybean oil find extensive use in the preparation of cooking fats. As indicated above, these oils are characterized by the presence of esters of unsaturated acids. In order to change them to solids it is necessary only to hydrogenate them. This is accomplished by treating the oils with hydrogen in the presence of nickel. The reaction may be considered as involving the change of triolein to tristearin.



If the oil is allowed to react with enough hydrogen to effect complete saturation, the product is a hard, waxy solid. By interrupting the reaction before saturation is complete, a fat of the proper consistency for use as a substitute either for butter or for lard may be obtained. If it is to be used as a butter substitute it is churned with skimmed milk and otherwise flavored to increase its resemblance to butter. Pure vitamins or vitamin extracts may also be added. If the product is to be marketed in the summer it is made a little "harder" than that intended for winter use. The principal difference between natural butter and such substitutes is that the latter do not contain esters of the lower fatty acids. There is no difference in calorific value.

**Soaps and Detergents.** The common soaps are sodium salts of fatty acids. They are usually made by boiling a fat with sodium hydroxide solution. When the saponification is complete the reaction mixture is saturated with salt, which assists in the separation of the soap by reducing its solubility (common ion effect). The glycerol remains dissolved in the brine, from which it is separated by distillation. The following equation illustrates the saponification of a fat.



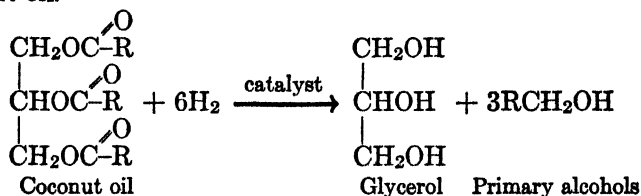
The composition of the soap depends upon the fat used in its preparation. An olive oil soap consists largely of sodium oleate, a coconut oil soap contains sodium laurate and various other salts (p. 105), and tal-

low soap is largely sodium palmitate and stearate. Various substances are added to the salts of the fatty acids for the preparation of soaps for different purposes. For example, naphtha soaps contain emulsified petroleum naphtha (p. 29) which is a solvent for fats, oils, and greases. Laundry soaps often contain salts of the rosin acids, which have detergent properties. The rosin acids are complex organic substances obtained from the sap of coniferous trees. Shaving soaps contain glycerol and gum to prevent rapid drying of the lather. Medicated soaps contain antiseptics, such as phenols (p. 157) and mercury salts. Most soaps contain about fifteen per cent of water.

**Insoluble Soaps.** The fatty acid salts of the alkali metals are soluble in water, but the salts of other metals are almost completely insoluble. The difficulties attending the use of soaps in hard water are known to everyone. Hard water contains salts of iron, magnesium, and calcium. When a soap solution is prepared in such water the first soap added is precipitated as the insoluble iron, magnesium, and calcium salts. Not only is soap wasted in this process, since the insoluble salts have no detergent action, but also the precipitates formed are difficult to remove from the objects being washed. They are particularly objectionable in the textile industry, since their presence in a cloth may cause it to be dyed unevenly.

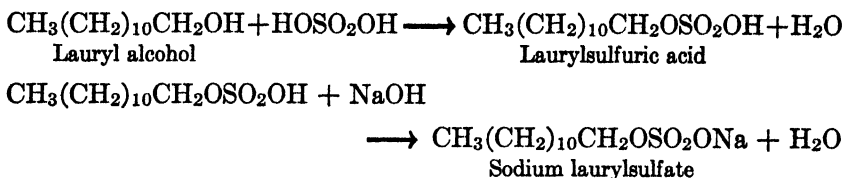
Some of the insoluble soaps are useful. Lead, copper, and mercury soaps are used in ointments and disinfectants. Zinc stearate and zinc palmitate are employed in face powders and in ointments. Aluminum soaps are incorporated into waxes and polishes. Several of the insoluble soaps are used in waterproofing textiles and leathers.

**The Alkyl Sulfate Detergents.** Several detergents which are free from the disadvantages of soap used with hard water are now available. Most of them are salts of organic derivatives of sulfuric acid. The Gardinols, also sold under the trade name Dreft, are sodium alkyl-sulfates of the general formula  $\text{ROSO}_3\text{Na}$ . The long-chain alcohols needed for their preparation are obtained by the hydrogenation (p. 107) of coconut oil.

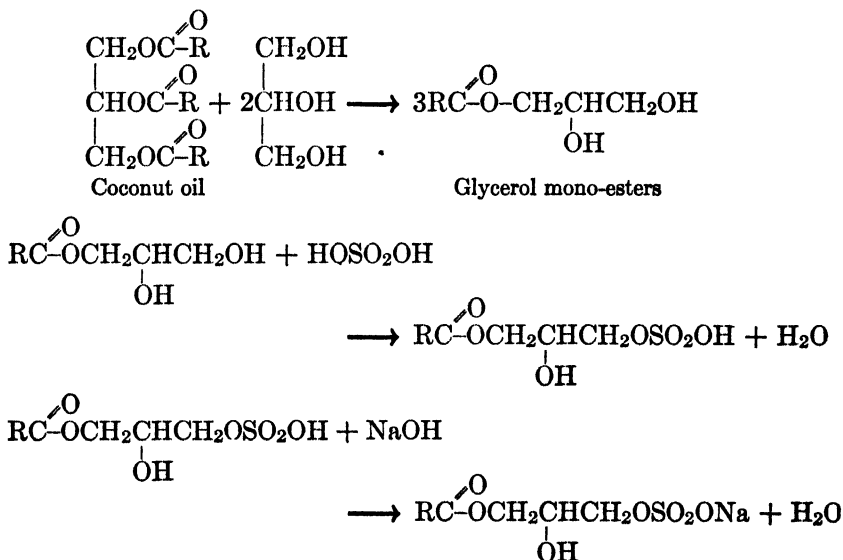


The product is a mixture of glycerol and the primary alcohols corresponding to coconut oil acids (p. 105). These are separated by distillation, and the lauryl alcohol is used in the preparation of the detergent.

*n*-Hexyl, *n*-octyl, and *n*-decyl alcohols are by-products. The lauryl alcohol is treated with sulfuric acid and the resulting acid ester is neutralized.



The product sold as Vel is prepared in a similar way from mono-esters derived from glycerol and the fatty acids. These are obtained by ester interchange (p. 92) from coconut oil and glycerol.



The iron, calcium, and magnesium salts derived from either of these detergents are soluble in water, hence either can be used in untreated hard water. For certain purposes they have a further advantage in that they can be used in weakly acidic solutions.

**Drying Oils.** Linseed oil, tung oil (China wood oil), and certain fish oils contain glyceryl esters of highly unsaturated fatty acids (p. 103). On exposure to air they change to tough, hard solids. The "dried" products are polymeric, so the drying must involve oxidation by the air and polymerization of the oxidation products. The process is catalyzed by metal oxides. Thus linseed oil as it is obtained from flaxseed changes only very slowly when spread out in the air, but if it is first



## PROBLEMS

1. Give equations for the conversion of isobutyl alcohol to: (a) isobutyric acid, (b) isovaleric acid, (c) isobutyl isovalerate, (d) isovaleryl chloride, (e) isovaleric anhydride, (f) isovaleramide, (g) isovalerophenone.

2. Give equations to illustrate the following terms: (a) esterification, (b) ammonolysis, (c) saponification, (d) transesterification, (e) Friedel-Crafts synthesis of hydrocarbons, (f) Friedel-Crafts synthesis of ketones.

3. Compare the formulas of stearic, oleic, linoleic, linolenic, ricinoleic, and eleostearic acids. Write equations for the conversion of each of the last five acids to stearic acid.

4. Compare the structural formulas of the sulfate detergents with that of a soap. What structural features appear to be necessary in a compound which is to be used as a detergent?

5. Assume that *n*-butyric acid, but not the chloride or anhydride, is available in the laboratory and *n*-butyrophenone is desired. Would you convert the acid to the chloride or to the anhydride in order to prepare the ketone? Explain.

## SUGGESTED READINGS

WURSTER, "Hydrogenation of Fats," *Ind. Eng. Chem.*, **32**, 1193 (1940).

STINGLEY, "Preparation of Drying Oils," *Ind. Eng. Chem.*, **32**, 1217 (1940).

## CHAPTER X

### AMINES

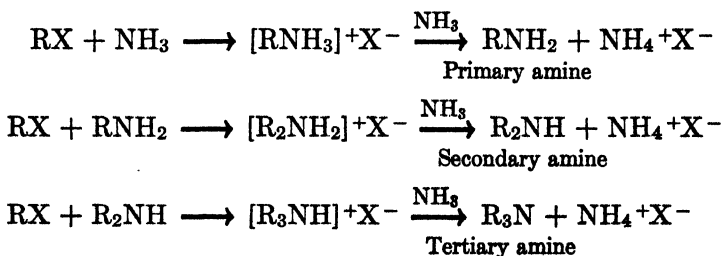
The amines may be regarded as derivatives of ammonia in which one, two, or three of the hydrogen atoms have been replaced by alkyl or aryl radicals. The amines are classified according to the number of such radicals present. Those in which only one organic residue is attached to the nitrogen atom are known as primary amines ( $\text{RNH}_2$ ).

Secondary amines  $\left( \begin{smallmatrix} \text{R} \\ >\text{NH} \\ \text{R} \end{smallmatrix} \right)$  have two organic radicals on the nitrogen atom and tertiary amines  $\left( \begin{smallmatrix} \text{R} \\ >\text{N}-\text{R} \\ \text{R} \end{smallmatrix} \right)$  have three.

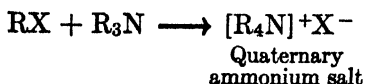
In Table XXII the names, classes, formulas, and boiling points of a number of amines are given.

#### Preparation of Amines

Amines can be made in a great variety of ways but scarcely any of the methods is generally applicable. That of Hofmann is perhaps the nearest approach to a general method. Hofmann found that alkyl halides react with ammonia to form primary, secondary, and tertiary amines. The following equations illustrate the course of the reaction:



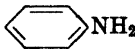
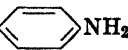
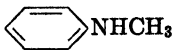
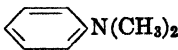
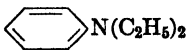
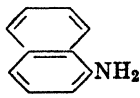
A fourth product is formed from the tertiary amine and the alkyl halide. It is known as a quaternary ammonium salt and may be regarded as an ammonium halide in which all four hydrogen atoms of the ammonium ion have been replaced by organic radicals.



The disadvantage of the Hofmann method is that it gives a mixture of products and the separation of a pure substance may be a difficult

TABLE XXII

## AMINES

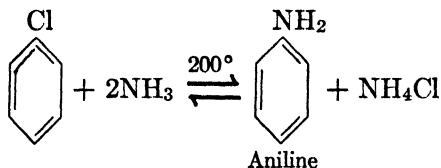
Name	Class	Formula	Boiling Point
Methylamine	Primary	$\text{CH}_3\text{NH}_2$	$-6.5^\circ$
Dimethylamine	Secondary	$(\text{CH}_3)_2\text{NH}$	7.4
Trimethylamine	Tertiary	$(\text{CH}_3)_3\text{N}$	3.5
Ethylamine	Primary	$\text{CH}_3\text{CH}_2\text{NH}_2$	16.6
Diethylamine	Secondary	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	55.5
Triethylamine	Tertiary	$(\text{CH}_3\text{CH}_2)_3\text{N}$	89.5
<i>n</i> -Butylamine	Primary	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$	77.8
Aniline	Primary	 $\text{NH}_2$	184.4
<i>p</i> -Toluidine	Primary	$\text{CH}_3$ -  $\text{NH}_2$	200 (m.p. $45^\circ$ )
Methylaniline	Secondary	 $\text{NHCH}_3$	195.7
Dimethylaniline	Tertiary	 $\text{N}(\text{CH}_3)_2$	193.5
Diethylaniline	Tertiary	 $\text{N}(\text{C}_2\text{H}_5)_2$	215.5
$\alpha$ -Naphthylamine	Primary	 $\text{NH}_2$	301 (m.p. $50^\circ$ )

problem. The boiling points of the ethylamines are far enough apart (see Table XXII) to permit separation by fractional distillation, and the method is used commercially to prepare all three amines from ethyl chloride and ammonia.

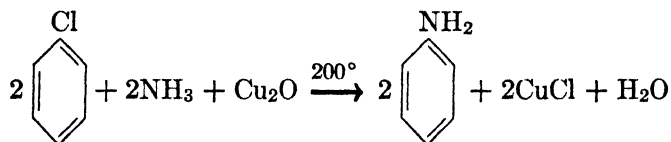
The Hofmann reaction is generally useful as a laboratory method only with primary alkyl halides. However, by employing drastic conditions it can be employed with aryl halides. One of the commercial methods for the preparation of aniline makes use of the reaction which occurs



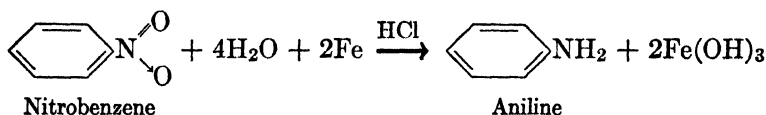
when chlorobenzene and ammonia are heated to about  $200^{\circ}$  under pressure. Under the conditions required, the reaction is reversible.



However, by addition of cuprous oxide to destroy the ammonium chloride it can be made irreversible. The cuprous chloride formed is treated with alkali to regenerate the oxide for the next run.

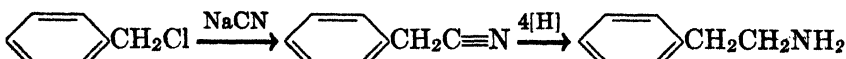


Among the most important general methods for the preparation of amines are those involving the reduction of nitrogen compounds of other types. For example, the classical method of preparing aromatic primary amines is the reduction of nitro compounds. Until the development of the chlorobenzene process, the reduction of nitrobenzene by the action of iron and a trace of acid was the only commercial preparation of aniline.

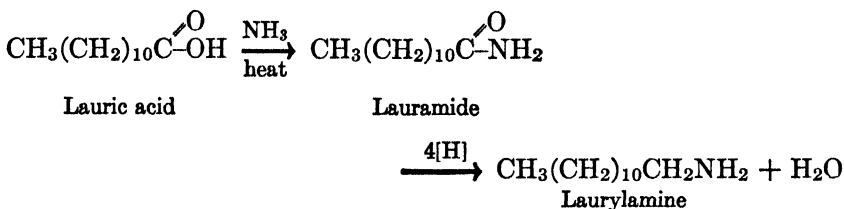


This preparation is still carried out in industry. Aliphatic nitro compounds also can be reduced to primary amines. The lower nitroparaffins which have recently become available (p. 12) thus provide a source of methyl-, ethyl-, *n*-propyl-, and isopropylamines.

A method of importance in the preparation of aliphatic primary amines involves the utilization of acid derivatives. Nitriles and amides can be reduced to primary amines, either by hydrogen and a catalyst or by sodium and alcohol. The reduction of nitriles enables one to prepare primary amines from alkyl halides and at the same time add one carbon atom to the chain. An example is the preparation of  $\beta$ -phenyl-ethylamine from benzyl chloride by way of benzyl cyanide.



The reduction of amides provides a method for transforming an acid to a primary amine of the same number of carbon atoms. The conversion of lauric acid to laurylamine is an example.

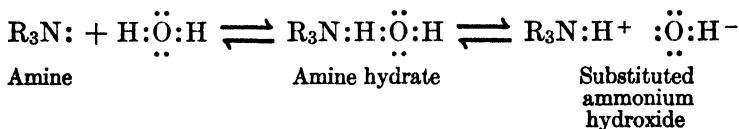


The same result could be achieved by dehydrating the amide to the nitrile and reducing the latter.

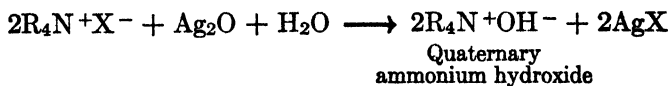
Other methods for the preparation of primary amines, and of secondary and tertiary amines, are discussed in Chapter XXIX.

### Reactions of Amines

**Hydration.** Amines are more soluble in water than are the alcohols of corresponding molecular weights. Certain tertiary amines exhibit the peculiar behavior of being more soluble in cold than in hot water. These observations indicate that the amines form unstable hydrates which are more soluble than the amines. The hydration undoubtedly involves coordination between the nitrogen atom and a hydrogen atom of water.

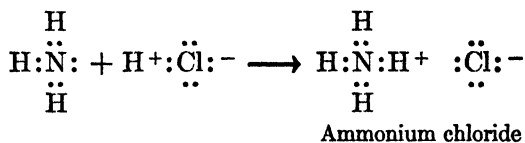


Ionization of the hydrate accounts for the basic properties of the amine. In this connection it is interesting to consider the basicity of quaternary ammonium hydroxides. These can be made from quaternary halides and silver oxide.

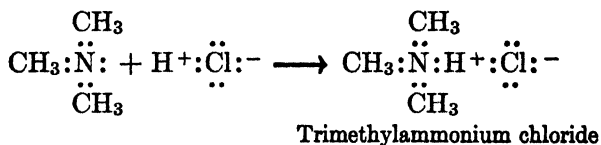
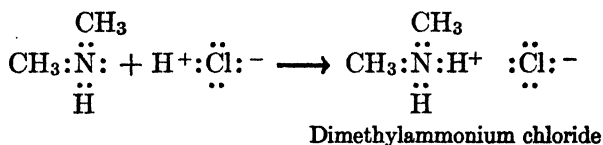
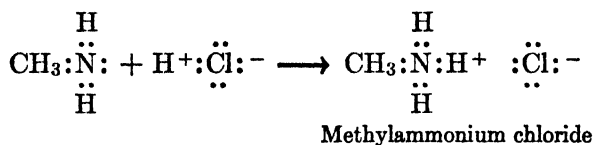


Here the hydroxyl group must remain as an ion, since the cation has no hydrogen atom capable of coordinating with it. As a consequence the quaternary hydroxides are extremely strong bases, comparable to the alkali hydroxides.

**Salts.** Most of the reagents which attack ammonia also react with the amines. The outstanding characteristic of ammonia and amines is basicity. The basic character of ammonia may be attributed to its tendency to donate its unshared pair of electrons to a deficient atom or ion. In the formation of ammonium salts from ammonia and acids the pair is accepted by a hydrogen ion.



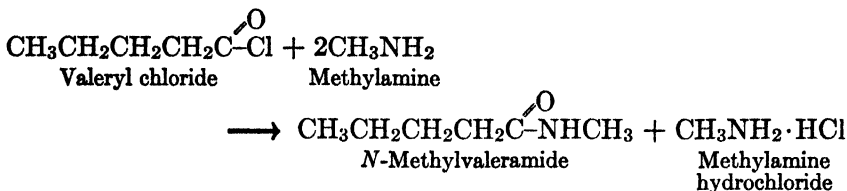
Primary, secondary, and tertiary amines react to form substituted ammonium salts. Methylammonium chloride, dimethylammonium chloride, and trimethylammonium chloride are obtained from methylamine, dimethylamine, and trimethylamine, respectively.



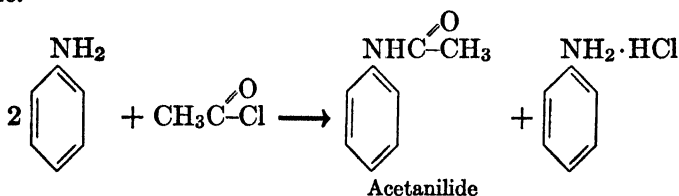
In order to simplify the writing of formulas, these products are ordinarily represented as  $\text{CH}_3\text{NH}_2 \cdot \text{HCl}$ ,  $(\text{CH}_3)_2\text{NH} \cdot \text{HCl}$ , and  $(\text{CH}_3)_3\text{N} \cdot \text{HCl}$ , respectively. To emphasize their relationship to the amines from which they are derived the salts are usually referred to as methylamine hydrochloride, dimethylamine hydrochloride, etc.

**Amides.** Primary and secondary amines react with derivatives of acids to yield amides. The most convenient laboratory methods of preparing amides employ acyl chlorides and acid anhydrides for the introduction of the acyl group. With chlorides of aliphatic acids it is necessary to employ two molecules of amine for each molecule of amide produced because the hydrochloric acid liberated from the reagent neu-

tralizes one molecule of the amine. The preparation of *N*-methylvaleramide is an example.

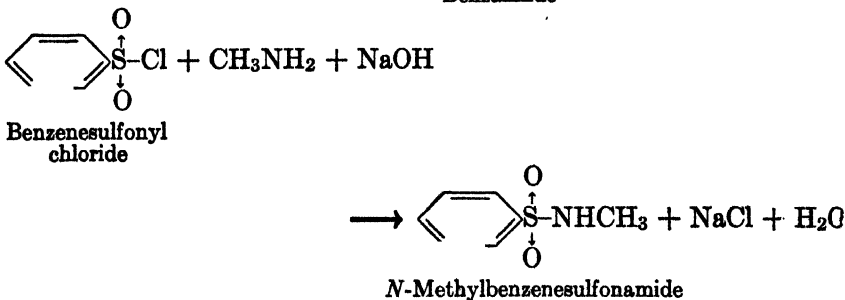
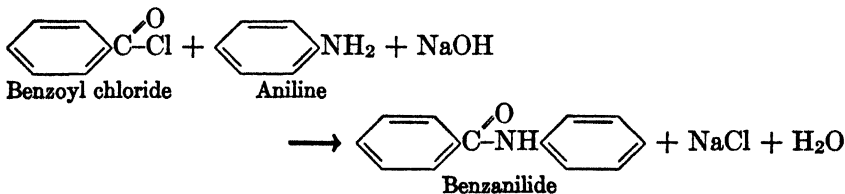


Acetanilide is prepared in a similar manner from aniline and acetyl chloride.



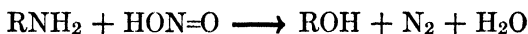
Acetanilide is useful in combating fever and is sold for this purpose under the name Antifebrin.

When the chlorides of aromatic acids or sulfonic acids are employed, it is possible to run the reaction in the presence of water and alkali. These chlorides react with amines much more rapidly than with water. The alkali combines with the hydrochloric acid, thus making it possible to convert all the amine to the amide. The process is known as the Schotten-Baumann reaction. The preparations of benzanilide and *N*-methylbenzenesulfonamide are examples.

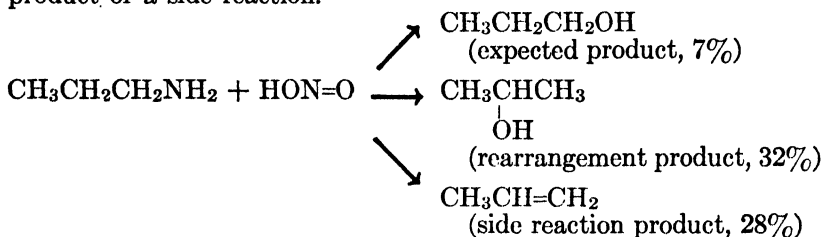


### Reactions of Amines with Nitrous Acid

Aliphatic amines can be classified on the basis of their reactions with nitrous acid. Primary aliphatic amines are converted to alcohols by this reagent.

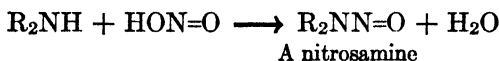


The reaction is of little value in the synthesis of alcohols from amines because of the tendency toward *rearrangement* during the replacement of the amino group by the hydroxyl group. Thus, treatment of *n*-propylamine with nitrous acid yields a mixture of propyl alcohol and isopropyl alcohol in a ratio of about 1 to 5. Propylene is also formed as the product of a side reaction.



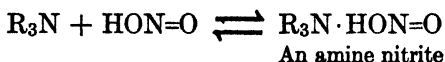
In testing an unknown aliphatic amine in this way the evolution of nitrogen gas is taken as an indication of the presence of a primary amine.

Secondary aliphatic amines react with nitrous acid to give nitrosamines.



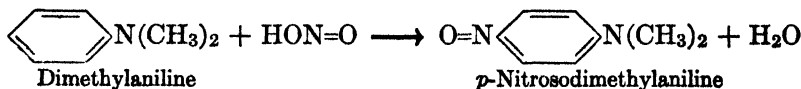
The nitrosamines are really amides of nitrous acid and as such would be expected to be neutral compounds. They usually separate from the test solution as neutral oils, insoluble in either acid or base.

Tertiary aliphatic amines react with nitrous acid to give unstable salts.



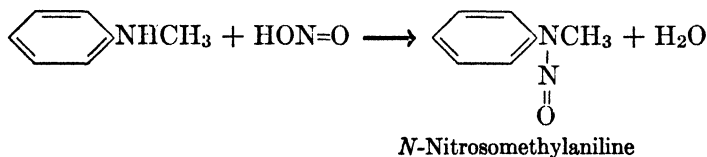
The free tertiary amine can be recovered from the nitrite by the addition of alkali.

Aromatic amines behave differently toward nitrous acid. Tertiary amines, such as dimethylaniline, react readily with nitrous acid to form *p*-nitroso derivatives.

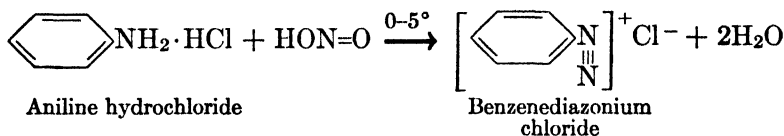


This reaction affords an illustration of the ease with which aromatic amines undergo substitution in the *ortho* and *para* positions of the ring. The amino group greatly alters the properties of the aromatic system. Dimethylaniline reacts with nitrous acid in water solution at room temperature, whereas the reaction of benzene with the more vigorous reagent, nitric acid, requires a higher temperature, a nearly anhydrous reagent, and a catalyst ( $\text{H}_2\text{SO}_4$ ).

Secondary aromatic amines react with nitrous acid to form nitrosamines, just as do the aliphatic analogs. For example, methylaniline yields *N*-nitrosomethylaniline.



The importance of primary aromatic amines in industrial and laboratory syntheses depends largely on their reaction with nitrous acid. Primary aromatic amines are converted to *diazonium* salts by treatment with nitrous acid in the presence of a mineral acid. The *diazotization* of aniline is an example.

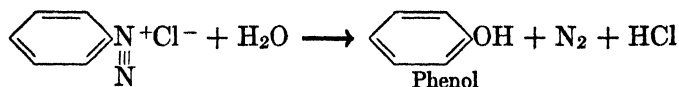


Since nitrous acid is unstable, sodium nitrite is added to an acid solution of the amine salt. The reaction is very rapid. An aqueous solution of sodium nitrite is added slowly until starch-potassium iodide paper indicates an excess of nitrous acid. In general, it is unwise to over-run the end point since free nitrous acid acts as an oxidizing agent.

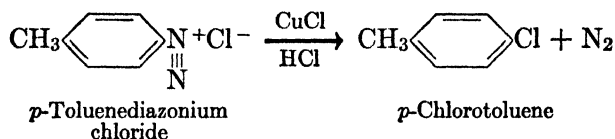
If the diazotization is carried out in alcoholic solution by adding an alkyl nitrite, the pure diazonium salt may be isolated. It can be thrown out of alcohol solution by the addition of ether. The pure salts are colorless, explosive solids. They are rarely isolated, but are used in aqueous solutions. On account of their instability, their solutions must be kept cold. Their instability seems to be due to the tendency of the two nitrogen atoms to separate as molecular nitrogen.

The reactions of diazonium salts can be classified in three general types, replacement of the diazonium group by other atoms or groups, coupling reactions, and reduction.

**Replacement Reactions.** If an aqueous solution of a diazonium salt is warmed, a *phenol* is produced. Benzenediazonium chloride yields phenol.

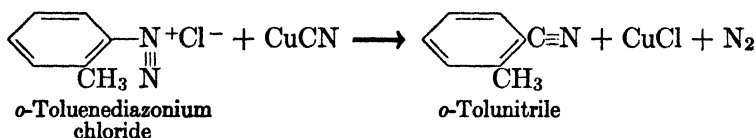


The diazonium group can be replaced by a halogen atom by warming a diazonium halide with a solution of cuprous halide and halogen acid. This is the *Sandmeyer reaction*. It is illustrated by the formation of *p*-chlorotoluene from diazotized *p*-toluidine.



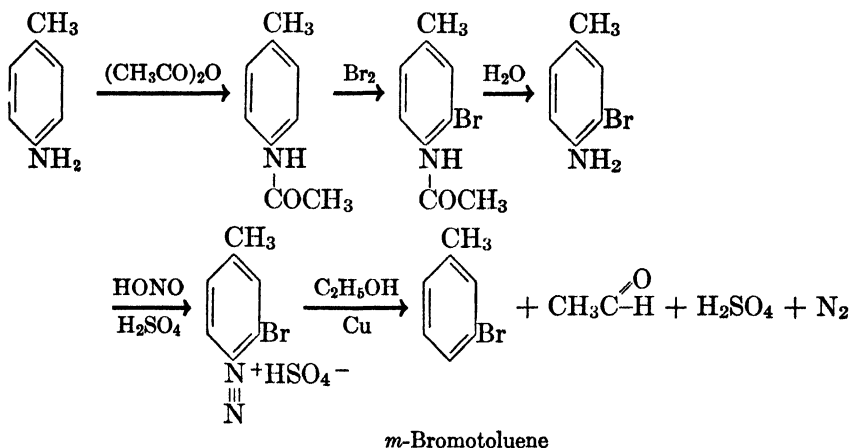
The *Gattermann* method differs by the use of metallic copper as the catalyst. The diazonium group can be replaced by bromine by treating the diazonium bromide or sulfate with cuprous bromide and hydrobromic acid. Replacement by iodine can be effected by treating the diazonium sulfate with iodine and potassium iodide in the absence of a catalyst.

Replacement of the diazonium group by the cyanide group is effected in much the same way. A diazonium chloride or sulfate is treated with a solution of cuprous cyanide. The preparation of *o*-tolunitrile from diazotized *o*-toluidine is an example.

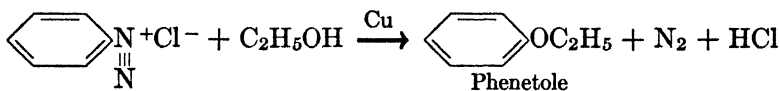


The diazonium group is replaced by a hydrogen atom when a diazonium salt is treated with a reducing agent such as ethyl alcohol in the presence of copper powder. The reaction is of value because it enables one to introduce an amino group and make use of its directive influence, and then remove the amino group. The synthesis of *m*-bromotoluene is illustrative. This compound can be obtained only in slight amount by the bromination of toluene and its synthesis would at first appear difficult. However, both *o*- and *p*-nitrotoluene can be obtained in the pure state from the nitration of toluene. From them both *o*- and *p*-toluidine are available by reduction. If it were possible to brominate *p*-toluidine the bromine would enter the ring *ortho* to the amino group (*meta* to the methyl group). Removal of the amino group, by diazotization and treatment with alcohol, would then produce *m*-bromotoluene

In practice one modification of this scheme is found necessary. If *p*-toluidine is brominated directly both the positions *ortho* to the amino group are attacked, because of the powerful effect of the amino group in activating the *ortho* and *para* positions toward substitution (p. 232). If the amine is first acetylated the bromination can be controlled, and the acetyl group can be removed by hydrolysis. The various steps in the synthesis of *m*-bromotoluene from *p*-toluidine are as follows:

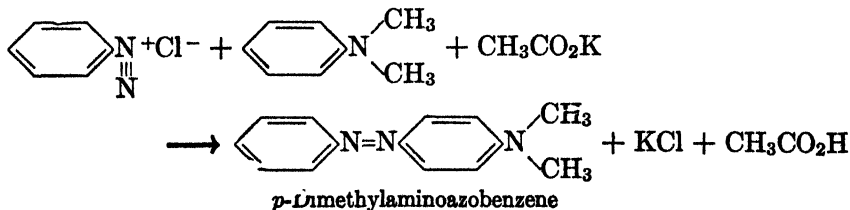


A side reaction which attends the use of alcohol and copper for the removal of the diazonium group is the formation of an ether. With benzenediazonium chloride the ether, phenetole, is the major product.



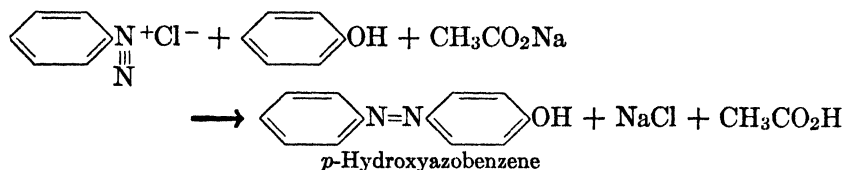
In many syntheses it is desirable to bring about the replacement of the diazonium group by hydrogen under the influence of reducing agents other than alcohol. The best reagents appear to be hypophosphorous acid and alkaline formaldehyde.

**Coupling Reactions.** When a diazonium salt is treated with an aromatic amine in the presence of a mild alkali, an azo compound is produced. The formation of *p*-dimethylaminoazobenzene from diazotized aniline, dimethylaniline, and potassium acetate is an example.



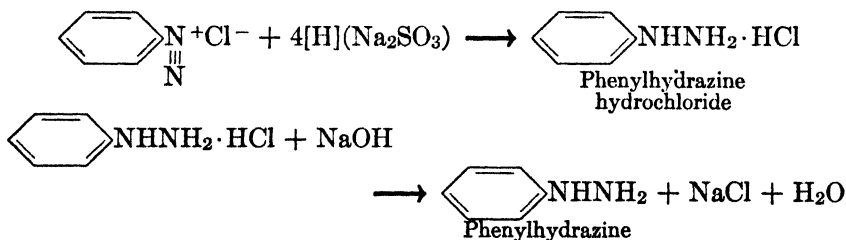


Phenols also couple with diazonium salts. The hydroxyl group of the phenols has an effect similar to that of the amino group in facilitating substitution in the *ortho* and *para* positions. Phenol, benzenediazonium chloride, and sodium acetate yield *p*-hydroxyazobenzene.



Azo compounds are colored. The coupling reaction finds many important applications in the synthesis of dyes (p. 467). It is also used in the laboratory as part of a test for primary aromatic amines. The unknown amine is subjected to the action of nitrous acid and the resulting solution is added to an alkaline solution of  $\beta$ -naphthol. Since only primary aromatic amines can be diazotized, the appearance of a dye in the last step is proof that the unknown amine is a primary aromatic amine.

*Reduction* of diazonium compounds produces arylhydrazines. Phenylhydrazine is made by reducing benzenediazonium chloride with sodium sulfite.



## PROBLEMS

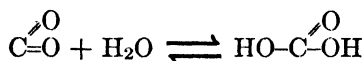
1. Suggest useful syntheses of the following: (a)  $\alpha$ -naphthylamine, (b) *n*-amylamine (from *n*-butyl alcohol), (c) *n*-octylamine (from caprylic acid).
2. Write equations for the reaction of aniline with: (a) acetic anhydride, (b) hydrochloric acid, (c) hydrochloric acid and sodium nitrite, (d) benzoyl chloride and aqueous sodium hydroxide.
3. Give equations to represent: (a) diazotization, (b) the Sandmeyer reaction, (c) coupling reaction.
4. By means of equations, show how toluene may be converted to: (a) *p*-nitrotoluene, (b) *p*-toluidine, (c) *p*-tolunitrile, (d) *p*-toluic acid, (e) *p*-iodotoluene.

## CHAPTER XI

### POLYFUNCTIONAL ACIDS

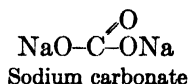
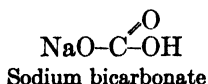
#### Carbonic Acid and Its Derivatives

Aqueous solutions of carbon dioxide are weakly acidic. From such solutions derivatives of carbonic acid can be prepared, although the acid itself never has been isolated because of the ease with which it decomposes to carbon dioxide and water.

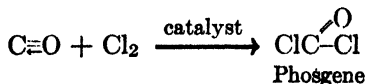


Carbonic acid is unique in containing two hydroxyl groups attached to the same carbonyl group. It is a dibasic acid, both hydrogen atoms being replaceable.

Carbonic acid forms two series of salts, the bicarbonates and the carbonates. Either may be obtained from an aqueous solution of carbon dioxide and an alkali. The formulas of the sodium salts are given as examples.



Other derivatives of carbonic acid, such as the chloride, esters, and the amide, are usually obtained from sources other than the acid. For example, the chloride,  $\text{COCl}_2$ , known as phosgene, is prepared from carbon monoxide and chlorine.

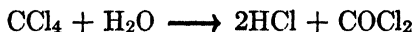


Light can be used as the catalyst, hence the name phosgene (light-generated). Phosgene is an extremely poisonous gas (b.p.  $8^\circ$ ) and has been used for military purposes. It has been said that inhalation for one-half hour of air containing as little as five parts per million of phosgene (by volume) may be fatal.

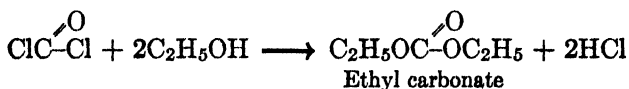
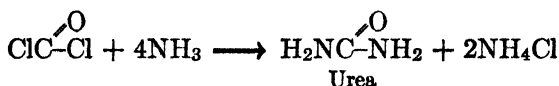
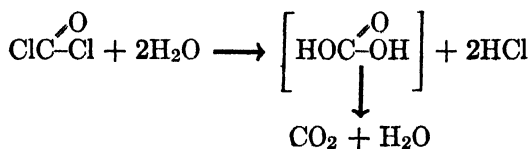
Phosgene is formed in small quantities when chloroform is exposed to air and light.



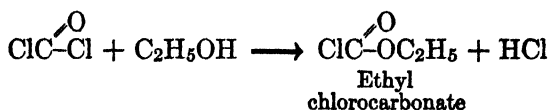
This fact militates against the use of chloroform as an anesthetic. Phosgene is also formed by the action of hot water on carbon tetrachloride. For this reason, a fire extinguisher employing carbon tetrachloride is dangerous when used in a confined space.



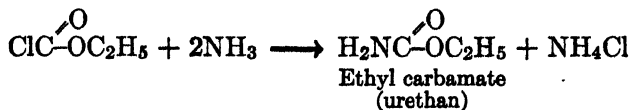
Phosgene has the chemical properties of an acyl chloride. It reacts with water, ammonia, and alcohol to form the acid, amide, and ester, respectively.



The reaction of the chloride with alcohol can be arrested at an earlier stage, yielding ethyl chlorocarbonate (also called ethyl chloroformate).

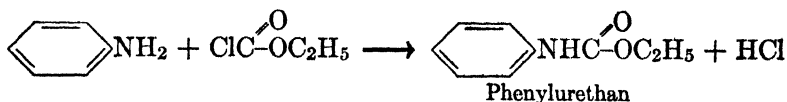


Ethyl chlorocarbonate is at once an acyl chloride and an ester. It reacts with ammonia to give an amido-ester, ethyl carbamate.

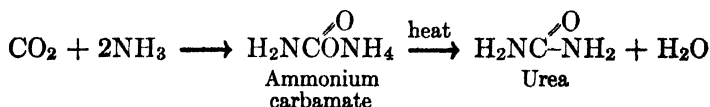


Carbamic acid ( $\text{H}_2\text{NC}-\overset{\text{O}}{\parallel}-\text{OH}$ ) is unstable but many of its salts and esters are well known. The ethyl ester is sometimes called urethan. It has been used in medicine as a hypnotic and sedative. Many of its derivatives in which organic groups are present on the nitrogen atom

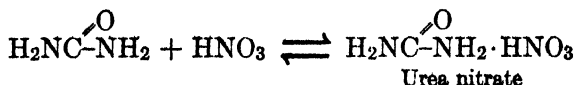
have similar properties. They may be made by treating amines with ethyl chlorocarbonate. Phenylurethan (or ethyl phenylcarbamate), for example, is obtained from aniline and the chlorocarbonate.



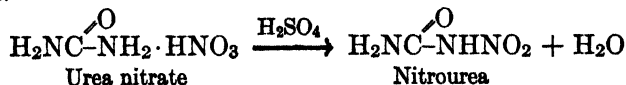
Urea, the diamide of carbonic acid, is of historical interest as the first organic compound to be synthesized from inorganic substances (p. 1). It is the end product of protein metabolism in man. Ammonia liberated from the proteins is combined with carbon dioxide in the liver, and the urea so formed is eliminated in the urine. Urea is now produced commercially for use as a special fertilizer and in the preparation of plastics and drugs. It is made from carbon dioxide and ammonia. These react to give ammonium carbamate, which can be converted to urea and water by heating.



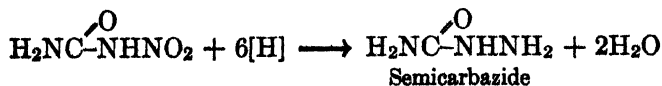
Unlike the simple amides, urea is a weak base. This might be expected from the consideration that two ammonia nitrogen atoms are attached to a single carbonyl group (p. 6). The salts of urea with strong acids are stable only in the presence of an excess of the acid or in the dry state. In contact with water they are hydrolyzed completely. Urea nitrate is an example.



When urea nitrate is added to cold sulfuric acid it is dehydrated to nitrourea.

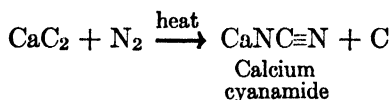


Semicarbazide, a reagent for aldehydes and ketones (pp. 73, 79), is prepared by the electrolytic reduction of nitrourea.



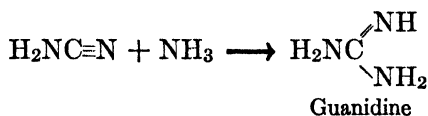


**Cyanamide.** The dehydration of urea yields cyanamide,  $\text{H}_2\text{NC}\equiv\text{N}$ , which may be regarded as the nitrile of carbamic acid ( $\text{H}_2\text{NC}-\overset{\text{O}}{\text{OH}}$ ). The most important derivative of cyanamide is calcium cyanamide. It is prepared from calcium carbide and nitrogen.

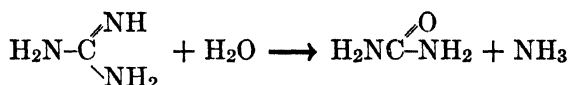


Calcium cyanamide is used in the fertilizer industry. It is also a raw material for the preparation of sodium cyanide and other chemicals.

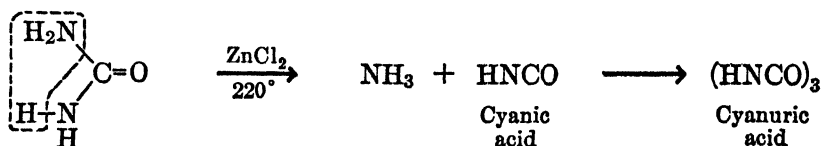
Guanidine may be prepared by the addition of ammonia to cyanamide.



Guanidine bears a formal resemblance to urea, but the third nitrogen atom greatly increases the basic strength. The basicity of guanidine is approximately that of the amines. Guanidine is very easily hydrolyzed to urea, particularly in the presence of bases.



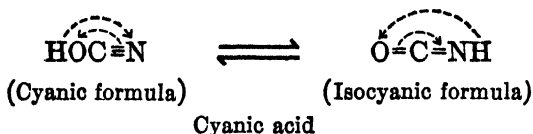
**Cyanic Acid, Isocyanic Acid, and Fulminic Acid.** When urea is heated with zinc chloride it loses ammonia and forms a gas which is called cyanic acid. The latter spontaneously changes to the trimer, known as cyanuric acid.



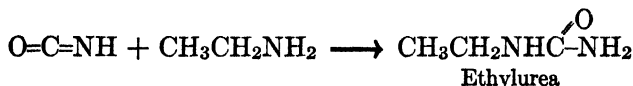
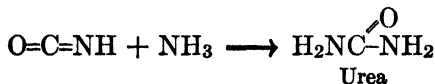
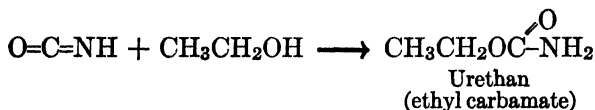
Cyanuric acid is depolymerized by heating and so may serve as a source of cyanic acid.

If cyanic acid is dissolved in water the resulting solution is strongly acid. For this reason the solution is believed to contain a substance of the formula  $\text{HOC}\equiv\text{N}$ , since this would be expected to be more acidic than the alternate structure,  $\text{O}=\text{C}=\text{NH}$ . On the other hand, its formation from urea and most of its reactions are more easily explained on the

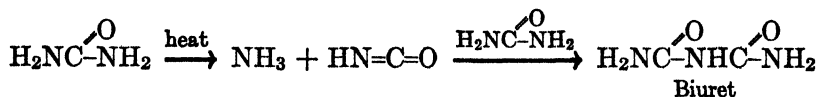
basis of the latter formula. It seems likely that the substance is actually a mixture of both forms in equilibrium.



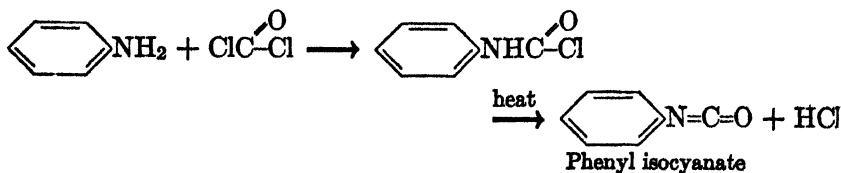
As indicated above, the reactions of cyanic acid are best represented on the basis of the isocyanic structure. Water, alcohols, ammonia, and amines react, as shown in the equations below.



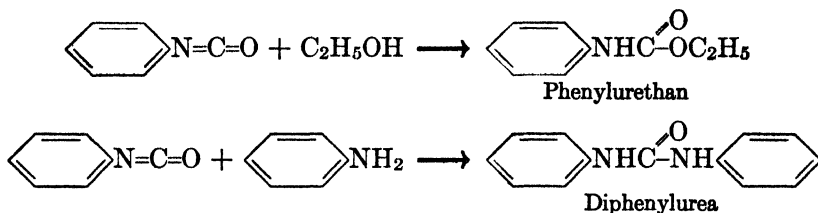
It is often convenient to carry out reactions of alcohols or amines with cyanic acid by heating the reagent with urea. The urea slowly decomposes to ammonia and cyanic acid, and the latter reacts with the reagent. It is possible that the formation of biuret ( $\text{H}_2\text{NC}-\overset{\text{O}}{\text{NHC}}-\overset{\text{O}}{\text{NH}_2}$ ) occurs in this way. It is formed along with ammonia when urea is heated alone. On the basis of the intermediate formation of cyanic acid the reaction would be represented as follows:



Organic derivatives of the isocyanic type are well known. One of the most useful is phenyl isocyanate, prepared from aniline and phosgene.

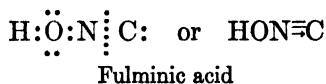


Its reactions resemble those of cyanic acid. For example, it reacts with alcohol to give phenylurethan and with aniline to give diphenylurea.



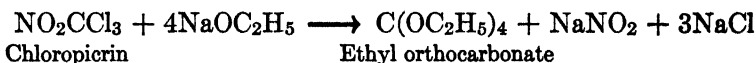
This and other isocyanates are used in the laboratory to convert amines and alcohols to solid derivatives.

*Fulminic acid* is an isomer of cyanic acid. Its structure is  $\text{HONC}$ , showing it to be related to the isocyanides (p. 209). The electronic formula is shown below.

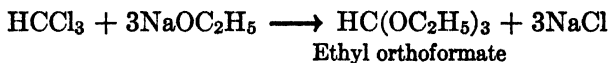


The mercury salt of fulminic acid is obtained from mercuric nitrate, nitric acid, and alcohol. Mercury fulminate is a powerful explosive, and because it detonates under a slight shock it is used in priming caps.

**Ethyl Orthocarbonate.** Carbon tetrachloride may be regarded as the chloride of the hypothetical orthocarbonic acid,  $\text{C}(\text{OH})_4$ . Esters of this acid are well known. They are usually made from chloropicrin (p. 373) and sodium alkoxides. The preparation of the ethyl ester is an example.



Similarly, chloroform may be considered the chloride of orthoformic acid. Orthoformic esters are made from chloroform and sodium alkoxides.



Higher orthoesters have the general formula  $\text{RC}(\text{OR}')_3$ . As the formulas indicate they are more closely related to the acetals than to the normal esters.

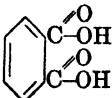
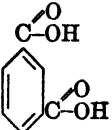
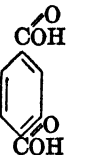
### The Dicarboxylic Acids

In Table XXIII are given the names, formulas, and melting points of the simpler acids containing two carboxyl groups. It is interesting to note that they are all solids and that any aliphatic member containing



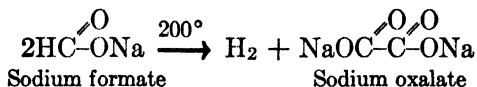
an even number of carbon atoms melts higher than the neighboring odd-carbon members.

TABLE XXIII

Name	Formula	Melting Point
<i>Aliphatic Dibasic Acids</i>		
Oxalic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{C}-\text{OH} \end{array}$	189°
Malonic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{CH}_2-\text{C}-\text{OH} \end{array}$	136
Succinic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{CH}_2-\text{CH}_2-\text{C}-\text{OH} \end{array}$	181
Glutaric	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{OH} \end{array}$	98
Adipic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{OH} \end{array}$	153
Pimelic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-(\text{CH}_2)_5-\text{C}-\text{OH} \end{array}$	105
Suberic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-(\text{CH}_2)_6-\text{C}-\text{OH} \end{array}$	144
Azelaic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-(\text{CH}_2)_7-\text{C}-\text{OH} \end{array}$	106
Sebacic	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-(\text{CH}_2)_8-\text{C}-\text{OH} \end{array}$	134
<i>Aromatic Dibasic Acids</i>		
Phthalic ( <i>o</i> -phthalic)		208 (dec.)
Isophthalic ( <i>m</i> -phthalic)		330
Terephthalic		(sublimes at 300°)

**Preparation of the Dibasic Acids.** Most of the simpler dibasic acids are prepared by special methods rather than by adaptations of the general methods for the introduction of the carboxyl group.

Sodium oxalate is prepared commercially by heating sodium formate. The reaction is a peculiar one involving the formation of hydrogen gas and the linking of the two carboxyl groups.



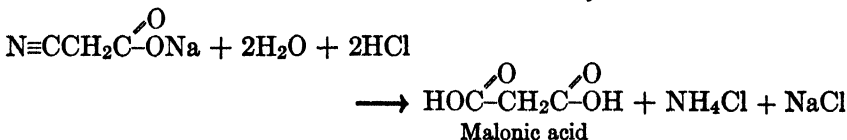
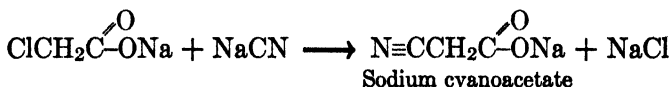
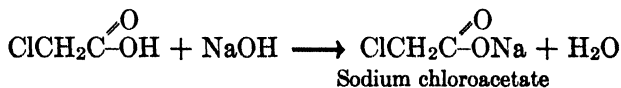
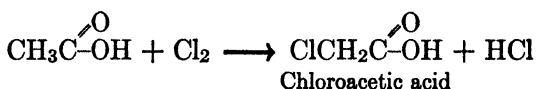
The free acid is obtained by converting the sodium salt to the calcium salt and treating the latter with just enough sulfuric acid to precipitate the calcium as calcium sulfate. Evaporation of the resulting aqueous solution yields oxalic acid dihydrate. Salts of oxalic acid can also be made by fusing sawdust (cellulose) with alkalis.

Oxalic acid is very easily oxidized to carbon dioxide and water. Even as mild an agent as a ferric salt (represented as ferric oxide in the equation) brings about the oxidation.



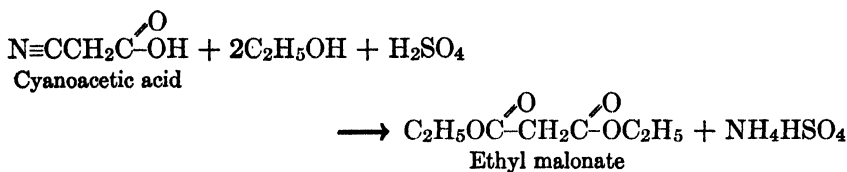
The use of oxalic acid in laundries for the removal of iron stains and ink spots depends on its reduction of ferric salts to soluble ferrous salts. Oxalic acid is also used in calico printing, in dyeing, and as a reagent in chemical analysis.

Malonic acid is prepared commercially from acetic acid by way of chloroacetic and cyanoacetic acids. The equations for the reactions are as follows:



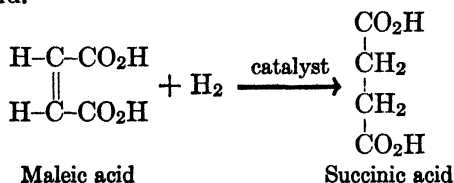
Malonic acid is less important as an industrial chemical than is its ethyl ester. The latter is used extensively in synthesis (p. 151) and in

the preparation of certain drugs (p. 154). It is prepared from cyanoacetic acid by the action of ethyl alcohol and sulfuric acid.



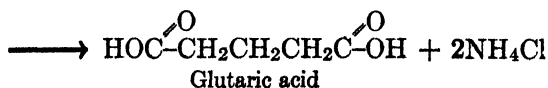
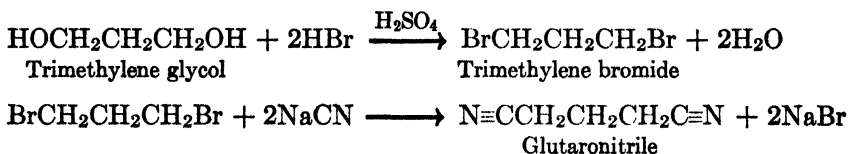
It should be noted that this conversion of the nitrile group to the ester group in a single operation is generally applicable and usually gives better yields than can be obtained by hydrolysis followed by isolation and esterification of the acid.

Succinic acid is most conveniently obtained by catalytic hydrogenation of maleic acid.

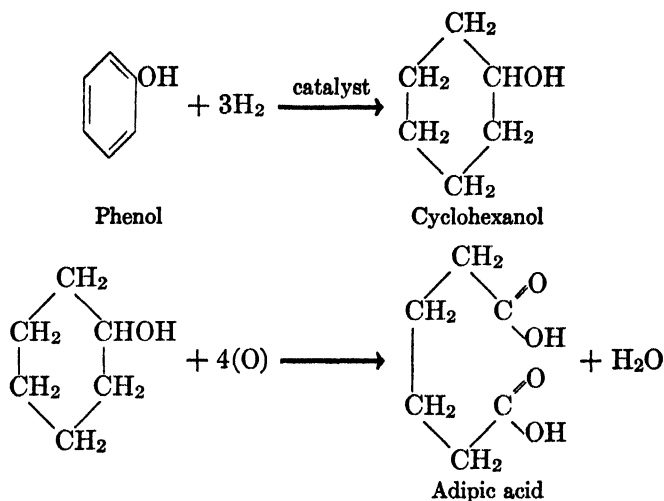


Maleic acid is available commercially from the catalytic oxidation of benzene (p. 147).

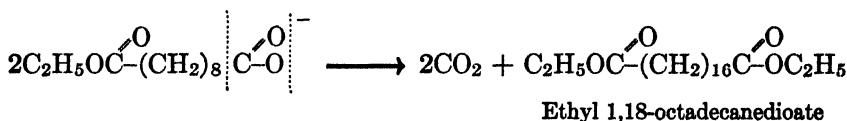
Glutaric acid is not a commercial chemical. One method of preparing it in the laboratory utilizes trimethylene glycol as the starting material. The bromide is prepared from the glycol and converted to the dinitrile by the action of a cyanide. Hydrolysis of the dinitrile yields the acid.



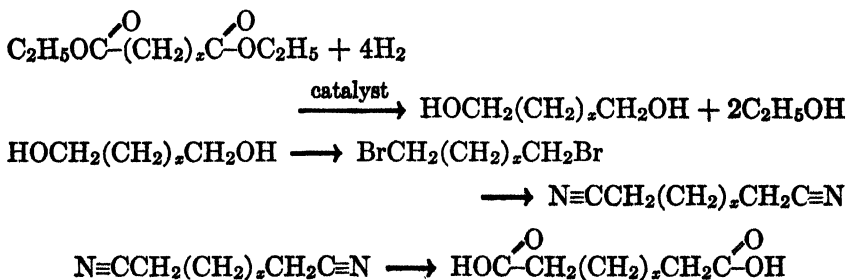
Adipic acid, as an intermediate in the manufacture of Nylon (p. 140), is one of the most valuable dibasic acids. It is prepared by oxidation of cyclohexanol. Cyclohexanol is obtained by the hydrogenation of phenol (p. 226).



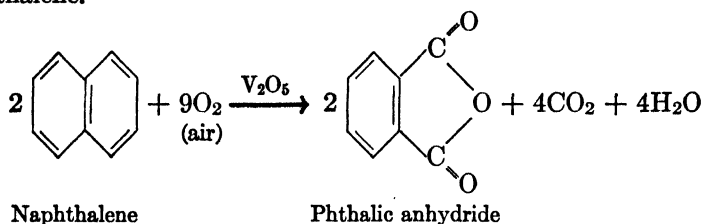
The higher dibasic acids are much less common than those discussed above, and their individual preparations will not be considered in detail. Pimelic acid is obtained from cyclohexanone by a series of reactions described later (p. 322). Suberic and azelaic acids are prepared by the oxidation of castor oil. Sebacic acid is obtained by heating castor oil with alkali. Still higher members may be made by the Kolbe electrolysis of the potassium salt of an acid ester. For example, the ethyl ester of 1,18-octadecanedioic acid is made from potassium ethyl sebacate.



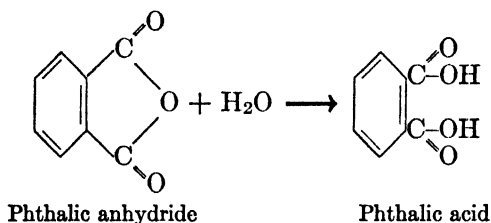
Another general method consists in the hydrogenation (p. 93) of an ester of a dibasic acid to yield a glycol which is converted to the dibasic acid of two more carbon atoms by the nitrile synthesis. The method is illustrated by the scheme outlined below.



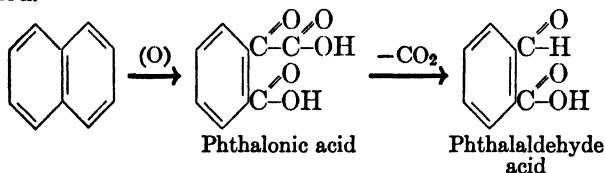
Of the aromatic dibasic acids, only phthalic acid is common. Its anhydride is prepared in large quantities by the catalytic oxidation of naphthalene.



The acid is prepared by hydrolysis of the anhydride.

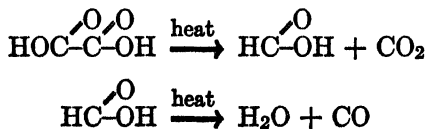


When naphthalene is oxidized with alkaline permanganate, phthalonic acid is formed.



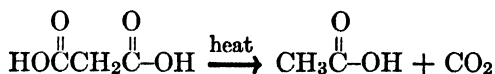
The latter compound can be decarboxylated easily and is thereby converted into phthalaldehyde acid.

**Behavior of Dibasic Acids on Heating.** The dibasic acids exhibit several different types of thermal decomposition. The distance between the carboxyl groups determines the nature of the reaction. If the carboxyl groups are in the 1,2 and 1,3 positions with respect to each other the dibasic acid easily undergoes decarboxylation. Thus, oxalic acid is converted to carbon dioxide and formic acid by heating at its melting point (189°). Formic acid is partly decomposed to water and carbon monoxide at this temperature, so the products actually obtained from oxalic acid are water, carbon monoxide, carbon dioxide, and formic acid.



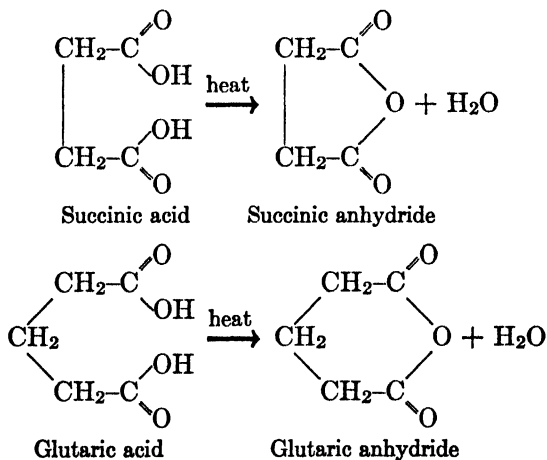
The decomposition occurs at lower temperatures when oxalic acid is heated with sulfuric acid. The products are then water, carbon monoxide, and carbon dioxide.

Malonic acid likewise loses carbon dioxide on heating to 150° or higher.



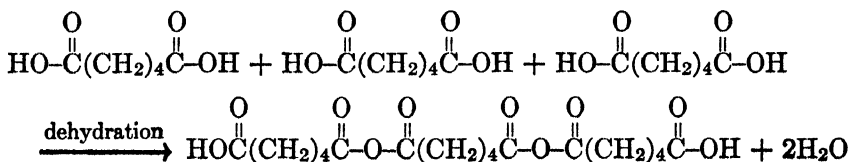
The monobasic acids undergo decarboxylation only under much more vigorous conditions. The carboxyl groups in oxalic and malonic acids activate each other. It will be seen later that other unsaturated groups have a similar activating influence on the carboxyl group when they are in the  $\alpha$  or  $\beta$  position with respect to it.

When the two carboxyl groups are in the 1,4 or 1,5 positions, the characteristic reaction is one of *dehydration*. The product is a cyclic anhydride containing five or six members in the ring. Both succinic and glutaric acids are converted to their anhydrides by heating to temperatures in the neighborhood of their melting points.

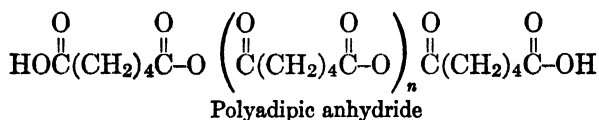


The ease with which these anhydrides are formed may be ascribed to the fact that the two carboxyl groups approach each other very closely. Models constructed from tetrahedral carbon atoms possess zigzag carbon chains; rotation of each carbon atom with respect to those to which it is joined (by thermal energy in the actual molecule) causes the hydroxyl groups of models of succinic and glutaric acids to collide. It is recommended that the student examine models for a demonstration of this point.

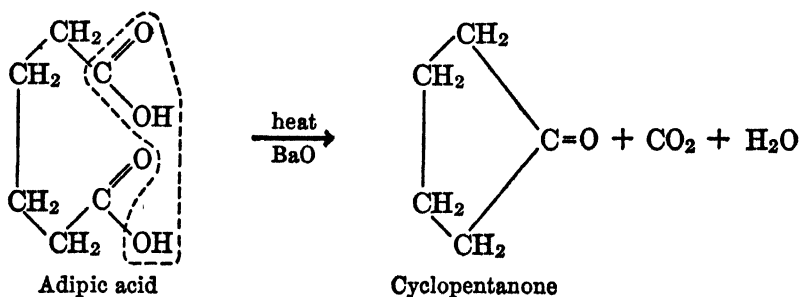
When the carboxyl groups of a dibasic acid are in more remote positions cyclic anhydrides are not readily formed. When adipic acid is heated with a dehydrating agent it forms a *polymeric anhydride* by loss of water between carboxyl groups of *different molecules*. The reaction can be illustrated as follows:



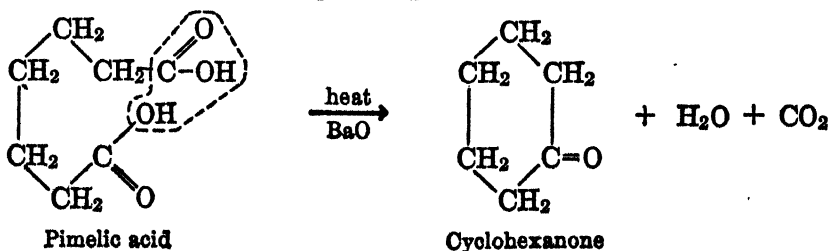
The polymer actually obtained has a molecular weight of several thousand; it can be represented by the following formula.



When adipic acid is heated in the presence of certain metallic oxides, such as barium oxide and thorium oxide, it undergoes loss of carbon dioxide and water to form cyclopentanone. The reaction is used for the laboratory preparation of the cyclic ketone.



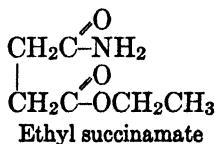
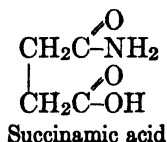
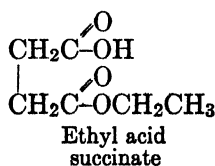
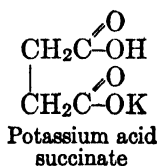
Pimelic acid is converted to cyclohexanone in good yields by this method, but the reaction is of no preparative value, since cyclohexanone is available from the reduction of phenol (p. 133).



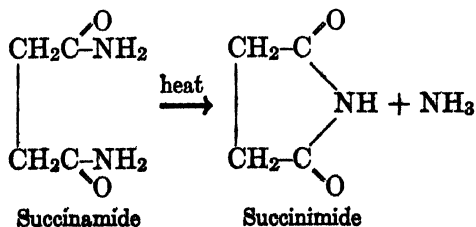
Cyclic ketones containing larger rings also may be obtained from the appropriate dibasic acids. However, the preparations are much less successful, from the standpoint of yields, than those of cyclopentanone and cyclohexanone. It is to be noted that in the preparation of both cyclic anhydrides and cyclic ketones the yields are best when the product contains a five- or six-membered ring. It is generally true that rings of this size are more readily formed than larger or smaller ones.

### Derivatives of Dibasic Acids

The carboxyl groups in the dibasic acids are capable of undergoing all the transformations described in connection with the monobasic acids. Thus, these acids yield esters, amides, chlorides, salts, and anhydrides. Since two carboxyl groups are present it is possible to prepare mixed derivatives, such as acid esters, amido acids, and amido esters. A few such derivatives of succinic acid are listed below.

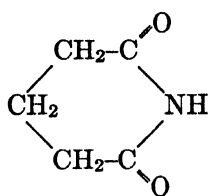


**Cyclic Imides.** Those dibasic acids which easily form cyclic anhydrides can be converted readily to imides. Imides are closely related to amides; they contain a nitrogen atom joined to two acyl groups. Succinimide can be obtained by heating succinamide, much as the anhydride can be obtained from the acid.

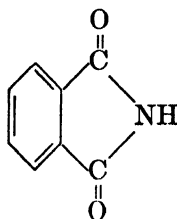




Glutarimide and phthalimide may be prepared in the same manner.

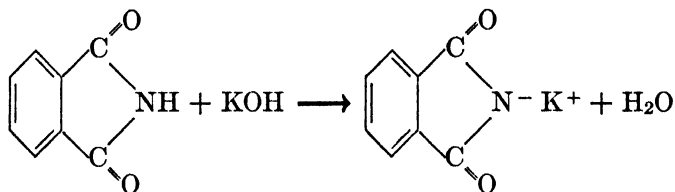


Glutarimide



Phthalimide

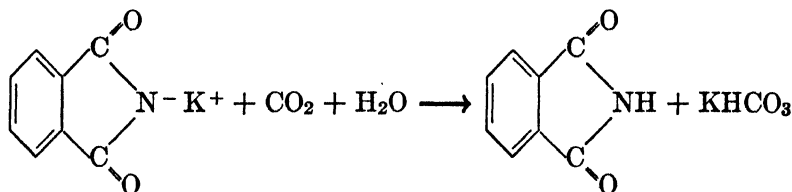
The most interesting property of imides is their acidity. It will be recalled that the amides, which contain one acyl group attached to a basic nitrogen atom, are neutral. The presence of the second acyl group on the nitrogen atom makes the imide a weak acid. The imides yield sodium or potassium salts on treatment with the corresponding alkali hydroxides.



Phthalimide

Potassium phthalimide

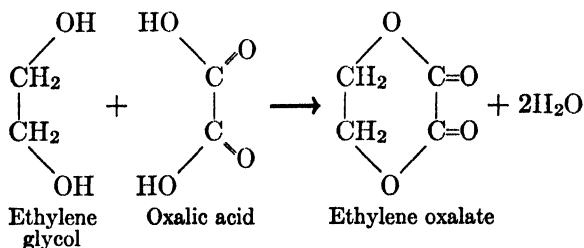
Since the imides behave as extremely weak acids such salts are decomposed by carbon dioxide.



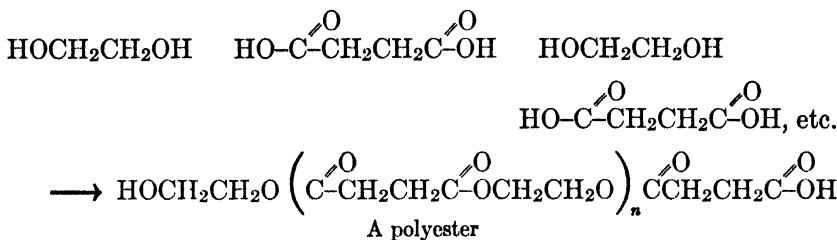
Potassium phthalimide

Phthalimide

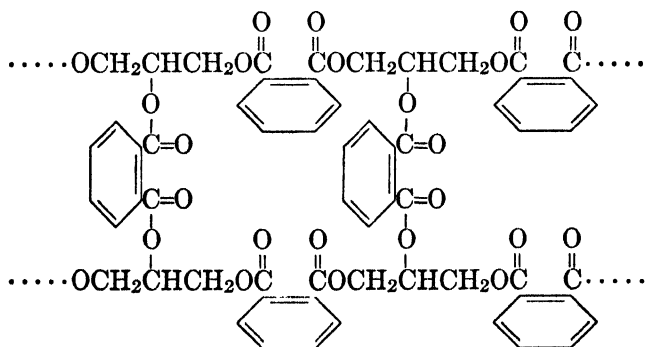
**Polyesters Derived from Dibasic Acids.** When a polybasic acid is allowed to react with a polyhydroxy alcohol the product may be either a cyclic ester or a polymeric ester. As might be predicted (p. 135), cyclic esters form when five- or six-membered rings are possible. Such cases are rare, since the simplest glycol and the simplest dicarboxylic acid yield a six-membered cyclic diester.



The products are usually polyesters. Ethylene glycol and succinic acid, for example, react to give a linear condensation polymer.



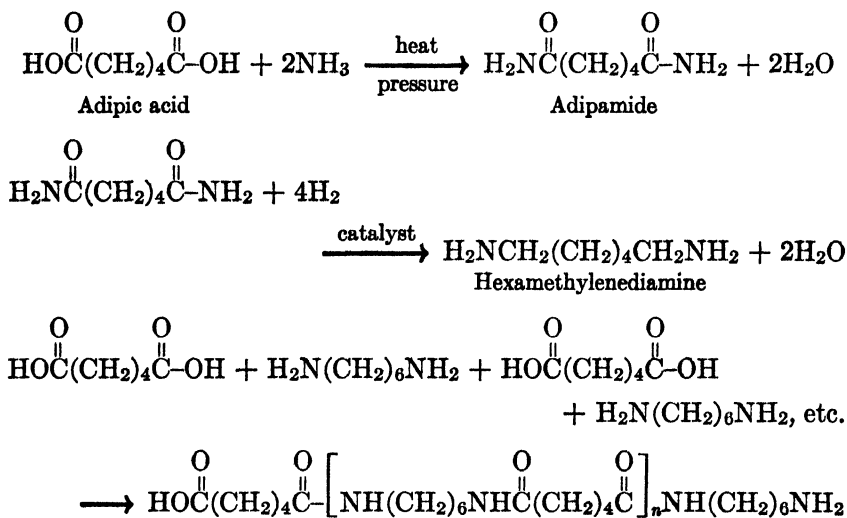
If glycerol is used in place of ethylene glycol the polymerization proceeds in all directions, yielding a three-dimensional polymer instead of a linear polymer. The most important polymers derived from glycerol are known as Glyptal resins; as the name indicates, they are formed from glycerol and phthalic anhydride. An idea of their structure can be gained from the following diagram:



This section of the structure of a glycerol phthalic anhydride polymer shows one way in which the long chains (the horizontal ones) are tied together through esterification of the third hydroxyl group of the glycerol residue. In the same way each of the horizontal chains is tied to others on all sides, giving the polymer three dimensions. If glycerol and phthalic anhydride are used alone the product is an insoluble, infusible,

brittle substance. These properties are characteristic of *cross linked* polymers (p. 126). To prevent the formation of the three-dimensional polymer an aliphatic acid is added in amount sufficient to esterify one of the three hydroxyl groups of the glycerol. Products so obtained are known as modified Glyptals. One of the most interesting is modified by addition of a fatty acid obtained from a drying oil, yielding an air-drying resin which is used in the preparation of high-grade enamels.

**Polyamides—Nylon.** When a dibasic acid is caused to react with a diamine under conditions suitable for amide formation, a condensation polymer is produced. Nylon is a polymer of this type, obtained from adipic acid and hexamethylenediamine. The latter is prepared from adipic acid by conversion to the amide and reduction of the amide or nitrile. Adipic acid is prepared from cyclohexanol, which in turn is made from phenol (p. 133). The equations for the preparation of Nylon from adipic acid are as follows:

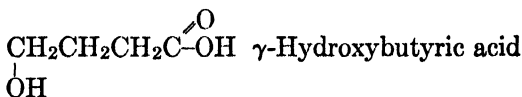
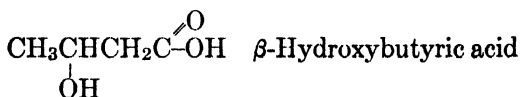
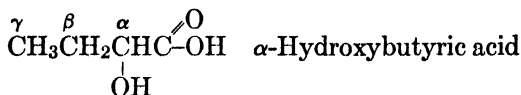


The molten polyamide is extruded in the form of fine filaments that are stretched by winding them from one reel onto another which rotates at a higher speed. The stretching process is believed to cause the long molecules, which are in random arrangement in the newly formed filament, to line up end to end and side by side. The strength and elasticity of the filament are greatly increased by the stretching. The filaments are then gathered together and made into a yarn. The textile obtained resembles silk but is superior to it in certain respects.

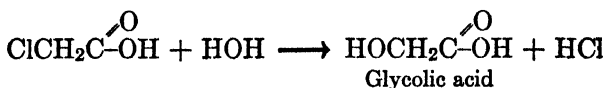
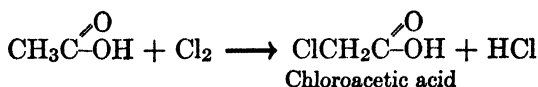
The polyamide is also produced in strands of fairly large diameter suitable for bristles.

### The Hydroxy Acids

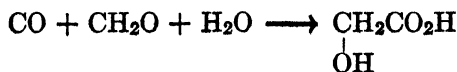
The hydroxy acids contain an alcoholic hydroxyl group as well as a carboxyl group. In general, they have all the properties of alcohols as well as those of acids. In addition they have certain special properties which vary with the distance between the two functional groups. Those in which the hydroxyl and carboxyl groups are on the same carbon atom are known as  $\alpha$ -hydroxy acids. The use of the Greek letters in naming substituted acids is evident from the names of the hydroxybutyric acids.



$\alpha$ -Hydroxy acids are sometimes made from the corresponding  $\alpha$ -halo acids. Thus glycolic acid may be obtained by treating chloroacetic acid with water in the presence of calcium carbonate.



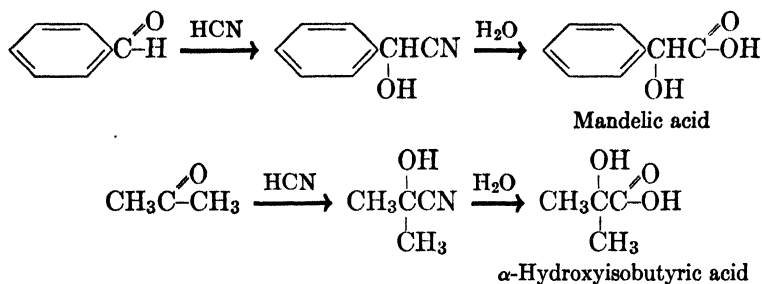
Glycolic acid is manufactured by the condensation of formaldehyde, carbon monoxide, and water in the presence of a catalyst such as sulfuric acid dissolved in an organic acid such as acetic acid. The condensation takes place under pressure and at a temperature of 160–170°.



If the water is replaced by methanol the product is methyl glycolate (p. 227).

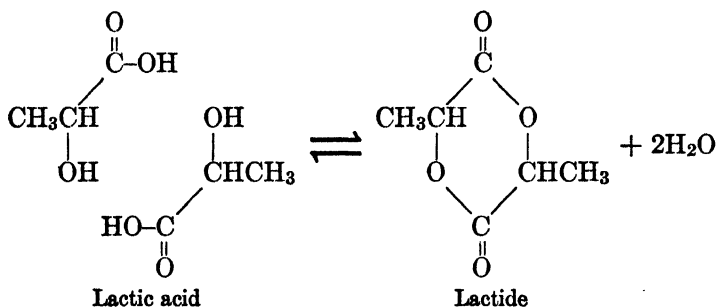
A very convenient synthesis of  $\alpha$ -hydroxy acids makes use of the cyanohydrins derived from aldehydes and certain ketones. Mandelic

acid and  $\alpha$ -hydroxyisobutyric acid are made in this way from benzaldehyde and acetone, respectively.



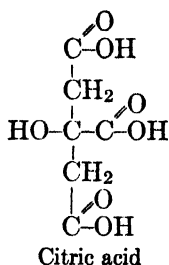
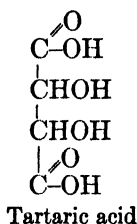
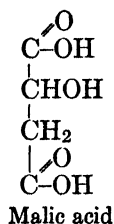
The most important  $\alpha$ -hydroxy acids are those obtainable from natural sources. The commonest of these is lactic acid,  $\text{CH}_3\text{CH}(\text{OH})\text{COOH}$ . It is intimately associated with certain of the chemical processes of life and is present in the blood and tissues, particularly in muscle tissue. It is formed from the sugar lactose in the souring of milk, hence the name lactic acid.

Since lactic acid is at once an alcohol and an acid it might be expected to react with itself to form an ester. Actually, when a water solution of the acid is evaporated to a concentration of 50 per cent or higher, part of the acid is converted to the dimeric ester, lactide.



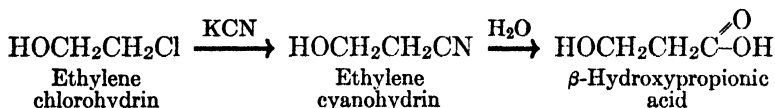
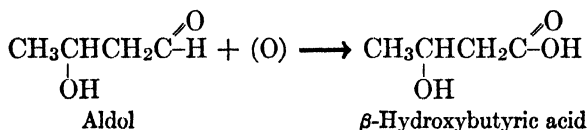
Other  $\alpha$ -hydroxy acids behave in the same way when subjected to dehydration.

Malic acid occurs in maple juice, in apples, and in other fruits. Tartaric acid, as the potassium acid salt, is obtained from argol or wine lees which are formed in the preparation of wine. Citric acid is a constituent of all citrus fruits. It is extracted from lemons and is also prepared by the action of molds on sugar solutions.

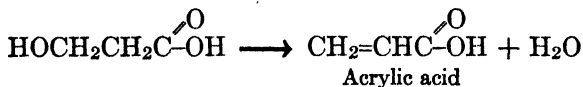


Lactic, malic, and tartaric acids each occur in isomeric forms which differ in their action on polarized light and are said to be optical isomers. This phenomenon is discussed in Chapter XIII.

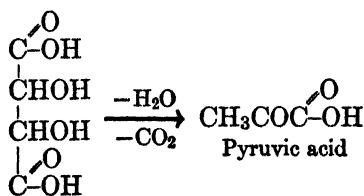
$\beta$ -Hydroxy acids usually are obtained by reduction of the corresponding ketonic acids or by means of the Reformatsky reaction (p. 276).  $\beta$ -Hydroxybutyric acid is made by the careful oxidation of aldol (p. 73).  $\beta$ -Hydroxypropionic acid can be obtained from ethylene chlorohydrin.



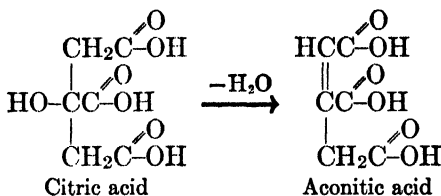
The  $\beta$ -hydroxy acids which contain a hydrogen atom on the  $\alpha$ -carbon atom are rather unstable. On heating they lose the elements of water, forming unsaturated acids.  $\beta$ -Hydroxypropionic acid, for example, yields acrylic acid.



Tartaric acid, when heated with sodium hydrogen sulfate, not only suffers the loss of water but also undergoes decarboxylation. The product is the simplest keto acid pyruvic acid.



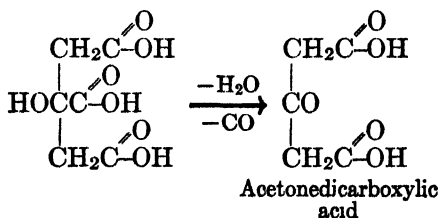
Citric acid also loses water at higher temperatures. The product is the corresponding unsaturated acid, aconitic acid.



If the decomposition is carried out by rapid distillation of the acid, decarboxylation occurs also, and the product is a mixture of the anhydrides of itaconic and citraconic acids.

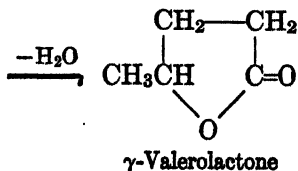
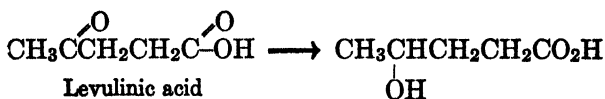


When citric acid is heated with sulfuric acid it loses water and carbon monoxide and yields acetonedicarboxylic acid.



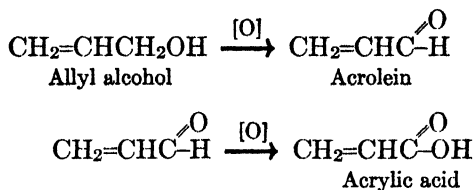
Loss of carbon monoxide and water is characteristic of  $\alpha$ -hydroxy acids.

$\gamma$ -Hydroxy acids are difficult to prepare. They lose water spontaneously to form inner esters known as lactones. For example, reduction of the keto acid levulinic acid (p. 282) yields  $\gamma$ -hydroxyvaleric acid, which readily forms  $\gamma$ -valerolactone.

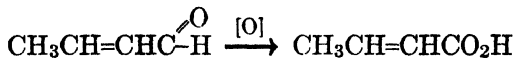


## Unsaturated Acids

The most common unsaturated acids are those which have the double bond between the  $\alpha$ - and  $\beta$ -carbon atoms. They are called  $\alpha,\beta$ -unsaturated acids. The simplest member of the series is acrylic acid, whose preparation from  $\beta$ -hydroxypropionic acid has been mentioned. It may also be obtained by the careful oxidation of allyl alcohol or acrolein.



Crotonic acid may be prepared by the oxidation of crotonaldehyde (p. 74).



There are two isomeric crotonic acids. One is a solid melting at  $72^\circ$  and the other a liquid of melting point  $15^\circ$ . Hydrogenation of either yields *n*-butyric acid, and ozonization of either gives acetaldehyde, so there can be no question but that the abbreviated structural formula given above represents each of them. The difference between the two isomers can be understood readily by constructing models with tetrahedral carbon atoms. It is found that the inclusion of a double bond results in a rigid structure and that it is impossible for one of the two atoms so joined to rotate with respect to the other. If the two groups attached to each unsaturated carbon atom are different from each other it becomes possible to make two models as shown in the diagram. The isomer in which the two like groups are on the same side is called the *cis* form, and that in which they are on opposite sides, the *trans* form. The two crotonic acids are such a pair; their formulas can be represented as follows:

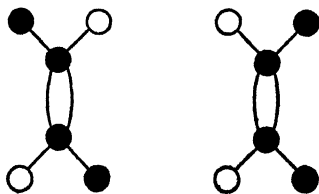
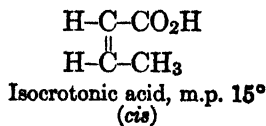
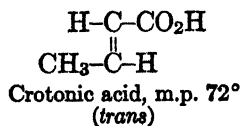


FIG. 1.

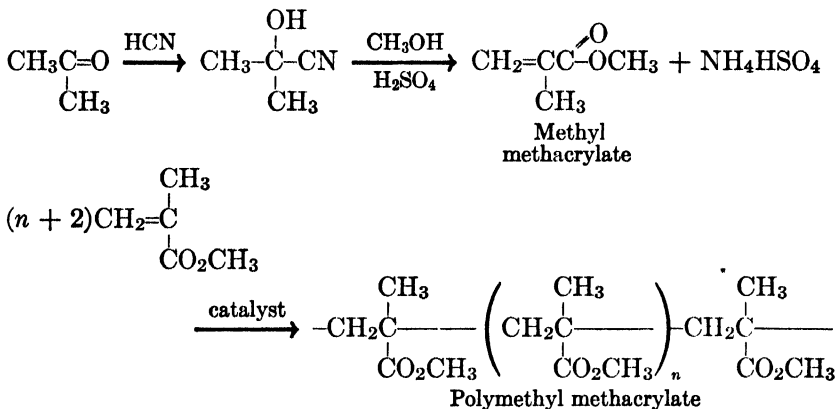




It is interesting to note that here the *trans* form is the higher melting. This is generally true of *cis-trans* pairs.

*cis-trans*-Isomerism is also called geometrical isomerism. It is a type of stereoisomerism (space isomerism), that is, the *cis* and *trans* forms differ in the space relationships within the molecules.

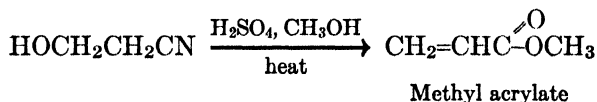
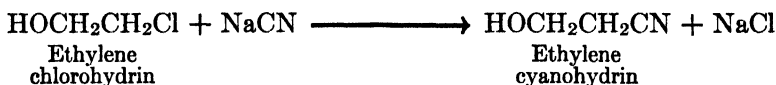
Methacrylic acid,  $\text{CH}_2=\text{C}(\text{CH}_3)\text{COOH}$ , is one of the most important unsaturated acids. It cannot exist in *cis-trans* modifications, since one of the unsaturated carbon atoms bears two identical groups (hydrogen atoms). The methyl ester is prepared from acetone cyanohydrin by treatment with methyl alcohol and sulfuric acid (p. 77). Methyl methacrylate is of value because it polymerizes readily.



The conversion of methyl methacrylate to polymethyl methacrylate can be accomplished by heat, by ultraviolet light, or by the action of organic peroxides. The polymer is more transparent than glass. It softens on heating and so can be molded. Because of its toughness, transparency, and lightness it is used in the windows of airplanes. Because it can be molded easily it finds many other uses, as in lenses, decorative fixtures, and even in dentures. It is sold under the trade names Lucite and Plexiglas.

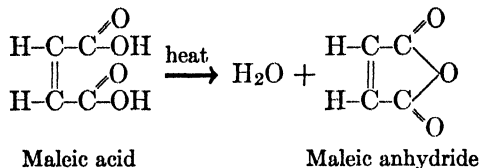
Polymethyl methacrylate has the peculiar property of conducting light along a curved path. Thus, when a flashlight is held against one end of a U-shaped rod of the material, the beam emerges from the other end, traveling in a direction opposite to its original course. Certain dental and surgical instruments make application of this phenomenon.

Methyl acrylate also polymerizes readily. It is made from ethylene chlorohydrin by way of the cyanohydrin.

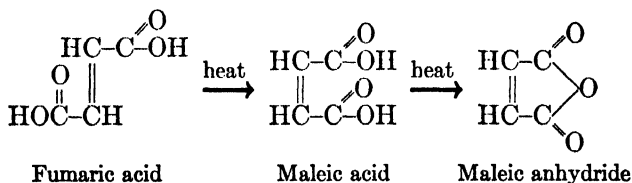


The polymer of methyl acrylate is much softer than that of methyl methacrylate. It is used in the finishing of textiles and leathers.

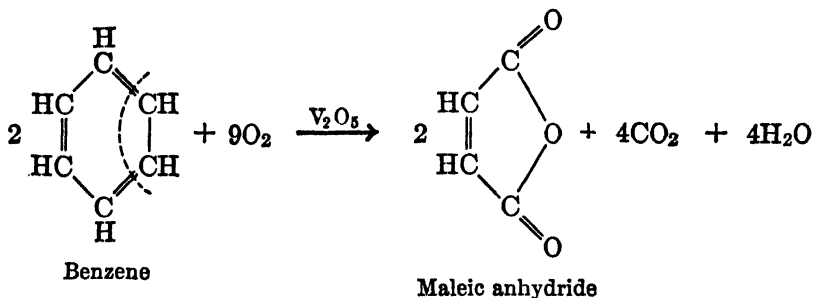
Maleic and fumaric acids are isomeric unsaturated dibasic acids. Maleic acid is the *cis* isomer and fumaric acid is the *trans* form. In this case it is easy to distinguish between the two isomers, since maleic acid readily forms an anhydride.



Fumaric acid is converted to an anhydride only under much more vigorous conditions. When heated to high temperatures it isomerizes to maleic acid and the latter yields maleic anhydride.

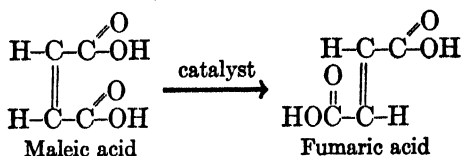


Maleic anhydride is prepared commercially by the catalytic oxidation of benzene.



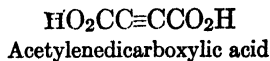
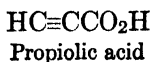
The acid is prepared by hydrolysis of the anhydride.

Fumaric acid is made by isomerization of maleic acid. Among the catalysts which bring about the change are sulfur and bromine.



Fumaric acid is found in many plants and is present in muscle tissue. The fact that fumaric acid is nontoxic and even occurs in living organisms, whereas maleic acid is a poison, affords a striking illustration of the differences which may exist in the physiological properties of *cis-trans* isomers.

Acetylenic acids are known also. Propiolic acid and acetylenedicarboxylic acid are examples.



Neither of these compounds exists in *cis-trans* modifications. The reason may be seen by examination of the following diagram of an acetylenic compound:

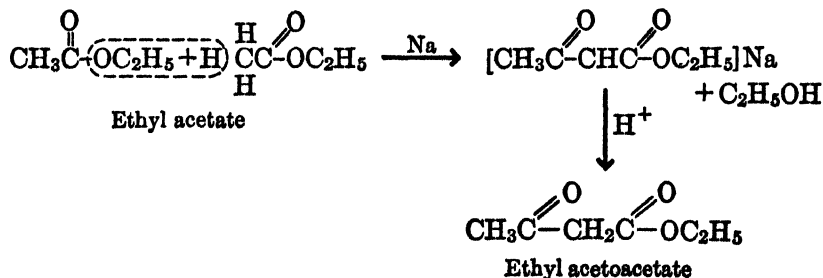


FIG. 2.

The four atoms shown in the acetylene model lie in a straight line; there are no alternative positions for the groups *a* and *b*.

### Keto Acids—Tautomerism

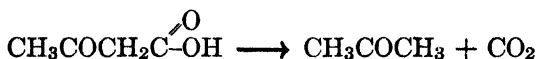
Ethyl acetoacetate is the ester of a  $\beta$ -keto acid. It has been known for many years as the product obtained by the action of sodium on ethyl acetate.



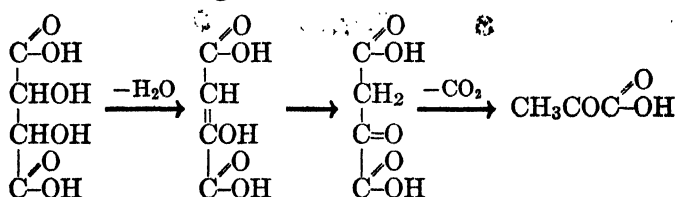
The ethyl alcohol reacts with the sodium to form sodium ethoxide. The latter appears to be the actual catalyst. Presumably, when sodium is used a small amount of sodium ethoxide is produced from a trace of alcohol present in the ethyl acetate. The reaction then starts, and more of the catalyst is produced from the alcohol formed. In reactions of this type it is frequently desirable to add a little alcohol, if sodium is being used, or to use dry sodium ethoxide as the catalyst. The reaction is known as the acetoacetic ester condensation. It is generally applicable

to esters of the formula  $\text{RCH}_2\text{C}(\text{O})\text{OC}_2\text{H}_5$ , yielding  $\beta$ -keto esters of the type  $\text{RCH}_2\text{C}(\text{O})\text{CH}(\text{R})\text{C}(\text{O})\text{OC}_2\text{H}_5$ .

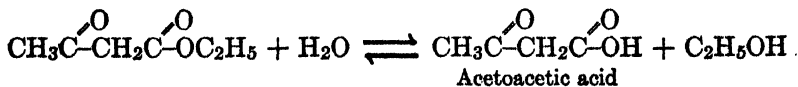
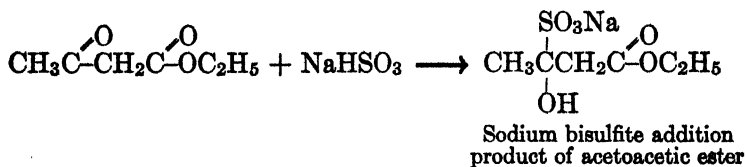
Acetoacetic acid is rarely prepared. It is unstable and undergoes decarboxylation to yield acetone and carbon dioxide.



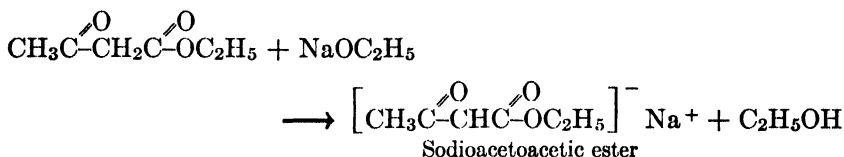
This type of reaction is characteristic of  $\beta$ -keto acids. The formation of pyruvic acid from tartaric acid (p. 143) probably involves a  $\beta$ -keto acid as an intermediate. The steps in this interesting transformation appear to be the following:



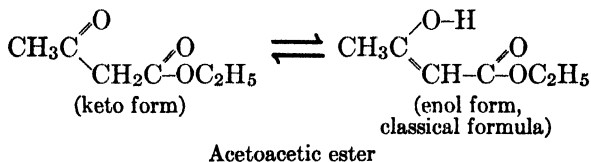
Ethyl acetoacetate, commonly known as acetoacetic ester, has properties which were puzzling to the chemists who first investigated it. As a keto ester, it would be expected to show the properties of ketones as well as those of esters. And, indeed, it does form carbonyl derivatives such as a sodium bisulfite addition product (p. 69) and also gives the reactions typical of esters, such as hydrolysis to an acid.



The curious fact is that a sample of the same lot of ester which gives the above reactions also behaves as a hydroxyl compound. For example, it gives a color with ferric chloride, a test which is characteristic of phenols (p. 160), and it can be converted to a sodium derivative by the action of sodium or sodium ethoxide.



In order to account for all these reactions it was proposed that ordinary acetoacetic ester is a mixture of two compounds, called the *keto* and *enol* forms.



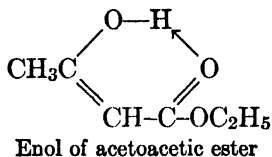
If it is postulated that the two forms are in equilibrium, then it is possible to explain all the reactions. A reagent, such as sodium ethoxide, which attacks the enol form causes the equilibrium to shift until all the material has been converted to an enol derivative. A carbonyl reagent shifts the equilibrium in the other direction so that the sample behaves as if it contained only the keto form. The phenomenon of reversible interconversion between isomeric forms has been named *tautomerism*. The forms in mobile equilibrium are said to be tautomers of each other. Thus, the enol form of acetoacetic ester is a tautomer of the keto form.

The sodio derivative was formerly considered to have a structure, corresponding to that of the enol, in which the hydrogen atom of the hydroxyl group is replaced by a sodium atom. Since the sodio derivative is an ionic salt this representation cannot be strictly correct. If the sodium is written as a cation, then the remainder must be written as an anion and the question of the location of the negative charge arises. It may be carried by the oxygen atom or by the carbon atom or it may be divided between them. For this reason the formula just shown will be used in the sequel, and no attempt to show the actual location of the negative charge will be made.

The correctness of the hypothesis with respect to the tautomeric forms of acetoacetic ester has been demonstrated by their separation. This can be accomplished by careful distillation in quartz apparatus. Glass

apparatus is to be avoided because alkali, always present in traces on the surface of glass, catalyzes the interchange of the two forms. The pure enol form has been found to possess all the chemical properties to be expected on the basis of the formula given above. It gives the enol reactions rapidly but does not react as a ketone except as it slowly tautomerizes. Likewise the pure keto form reacts readily as a carbonyl compound but responds only slowly to enol reagents. Either of the pure forms slowly changes to ordinary acetoacetic ester on standing. In the presence of a trace of alkali the change is rapid. The equilibrium mixture obtained from either form contains about 10 per cent of the enol.

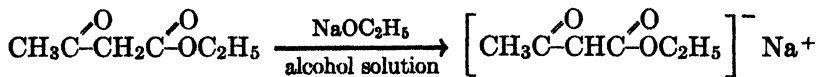
In the separation of the tautomeric forms of acetoacetic ester by distillation the enol form was found to be the lower boiling. At the time, this was a surprising observation, since ketones ordinarily boil lower than alcohols of similar structure (acetone, b.p. 56.1°; isopropyl alcohol, b.p. 82.3°). However, when it is recalled that the boiling points of alcohols are "abnormal" because of association (p. 45), a glance at the formula of the enol is sufficient to explain the apparent anomaly. The hydrogen atom of the hydroxyl group is so near the carbonyl oxygen of the ester group that coordination occurs between them, forming a chelate ring (p. 89).



The hydrogen atom of the hydroxyl group is thus not available for coordination with an oxygen atom of another molecule and consequently association does not occur. It is believed that chelation tends to stabilize the enol form. This would account for the fact that enols which are incapable of chelation, such as the hypothetical vinyl alcohol  $\text{CH}_2=\text{CHOH}$  (p. 23), have not been isolated.

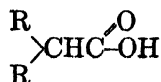
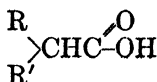
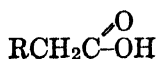
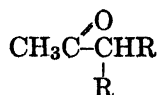
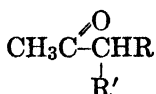
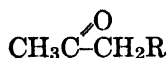
### The Use of Acetoacetic Ester and Malonic Ester in Synthesis

As indicated above, acetoacetic ester is readily converted to its sodio derivative. The latter can be *alkylated* by treatment with alkyl halides; either one or two alkyl groups can be introduced. The following general equations are illustrative.

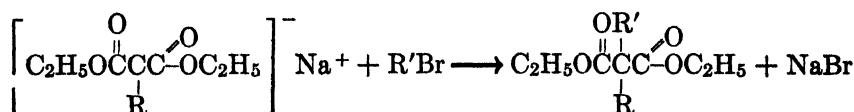
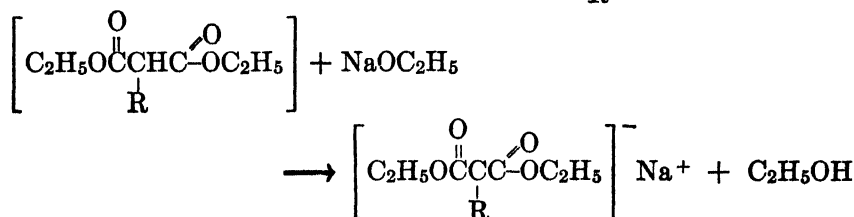
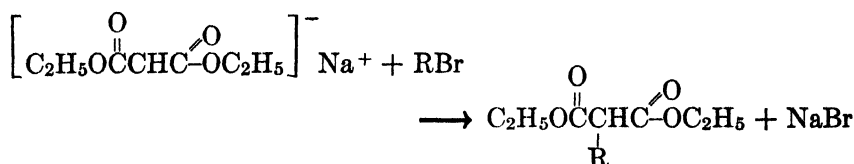
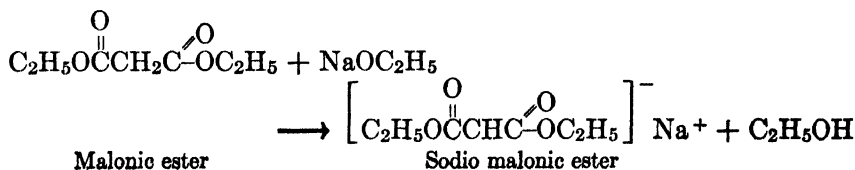




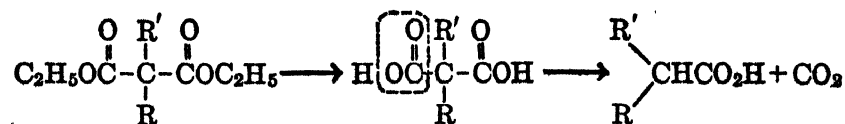
uents are attached to the same carbon atom and may be alike or different. These various products may be represented as follows.



In actual laboratory work it is more convenient to prepare the *acids* from malonic ester. Like acetoacetic ester, malonic ester yields a sodio derivative which reacts with alkyl halides.



Cleavage of the substituted malonic ester yields only the substituted acid. It is usually accomplished by saponification of the ester followed by isolation and decarboxylation of the malonic acid.

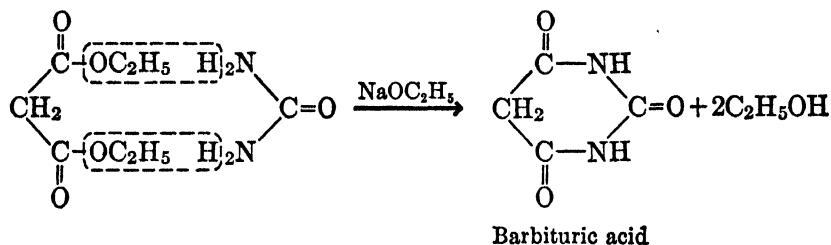




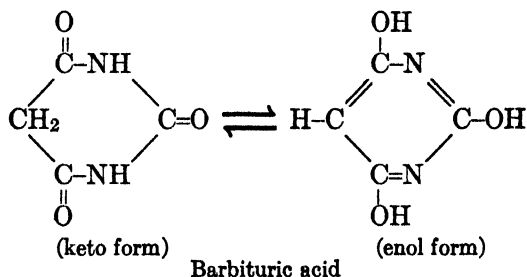
The substituted acetic acids so obtained are identical with those that can be prepared from acetoacetic ester. The advantage in the use of malonic ester lies in the fact that the yields are usually better, since the ketone cleavage which occurs as a side reaction in the acid cleavage of a substituted acetoacetic ester cannot occur in the corresponding malonic ester.

Aryl halides do not react with the sodio derivatives of acetoacetic and malonic esters and hence cannot be used in the syntheses indicated above. Among the alkyl halides those which are primary usually give excellent yields. Good results are obtained with secondary halide, but the yields from tertiary halides are negligible.

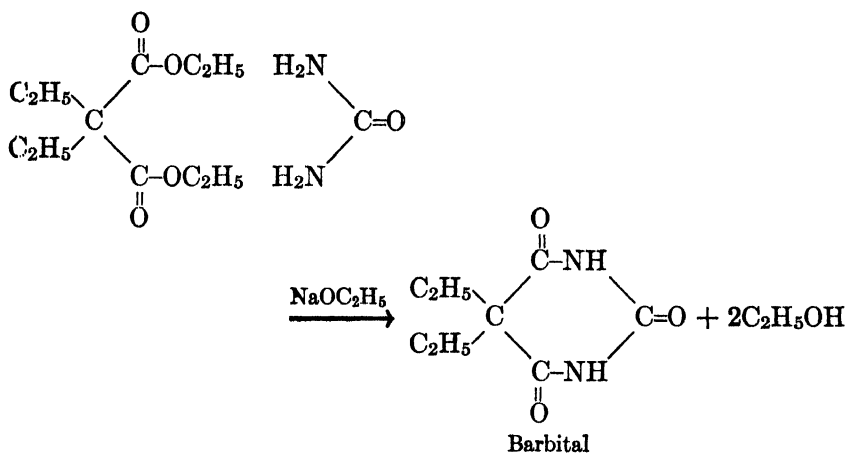
**Barbituric Acid and Its Derivatives.** When malonic ester and urea are brought together in the presence of sodium ethoxide they react by elimination of alcohol to form a cyclic substance known as barbituric acid.



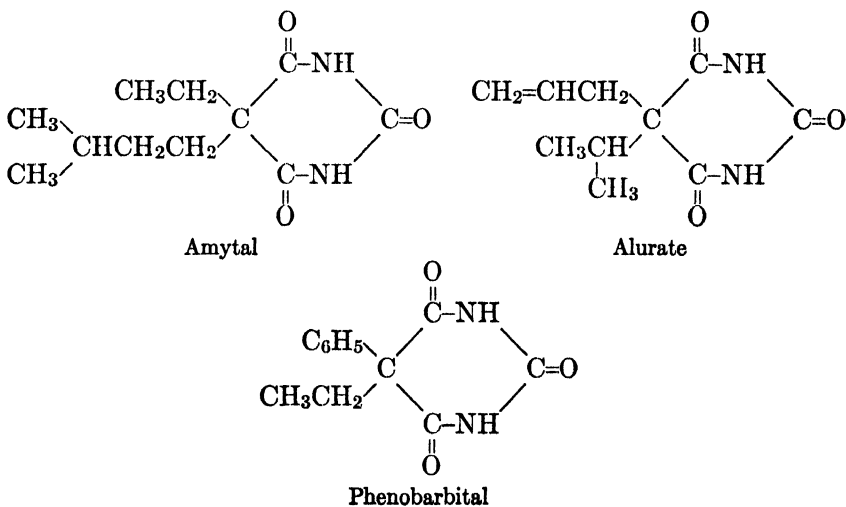
It will be noted that this compound is not a carboxylic acid. Its acidic property may be attributed to the presence of the two imide groups, or to the existence of an enol form.



Barbituric acid is a hypnotic and a sedative but in medicine it has been displaced by derivatives which are more effective. A great variety of derivatives have been prepared by alkylating malonic ester before condensing it with urea. For example, barbital (diethylbarbituric acid) is prepared from ethyl diethylmalonate and urea.



Other common barbiturates are amytal (isoamylethylbarbituric acid), alurate (allylisopropylbarbituric acid), and phenobarbital (phenylethylbarbituric acid), the formulas of which appear below.



## PROBLEMS

1. Give equations for commercial preparations of the following substances from coal, petroleum, and inorganic substances: (a) oxalic acid, (b) malonic acid, (c) succinic acid, (d) adipic acid, (e) urea, (f) Nylon, (g) barbituric acid, (h) phthalic acid.

2. By means of formulas or equations, illustrate the following: (a) condensation polymerization, (b) lactone, (c) lactide, (d) tautomers, (e) *cis-trans* isomers,

(f) imide, (g) cross linking, (h) polyester, (i) chelation, (j) enolization, (k) ketonization.

3. Give equations for the preparation of the following from acetoacetic ester, malonic ester, ethyl alcohol, and *n*-butyl alcohol: (a) caproic acid, (b) methyl *n*-amyl ketone, (c) di-*n*-butylacetic acid, (d) 2-ethylhexanoic acid.

4. Predict the effect of heating on: (a) methylmalonic acid, (b) phthalic acid, (c)  $\alpha$ -hydroxycaproic acid, (d)  $\beta$ -hydroxycaproic acid, (e)  $\gamma$ -hydroxycaproic acid, (f)  $\delta$ -hydroxycaproic acid, (g)  $\epsilon$ -hydroxycaproic acid, (h)  $\beta$ -ketocaproic acid, (i) succinamic acid.

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BOLTON, "The Development of Nylon" (Chemical Industry Medal Address), *Ind. Eng. Chem.*, **34**, 53 (1942).

HOFF, "Nylon as a Textile Fiber," *Ind. Eng. Chem.*, **32**, 1560 (1940).

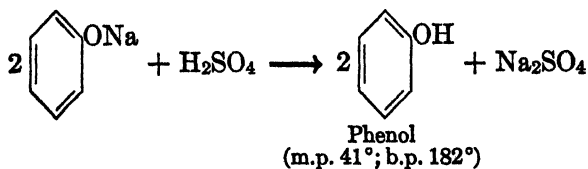
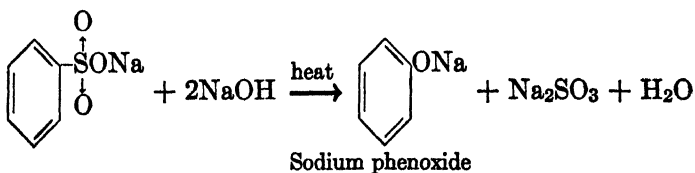
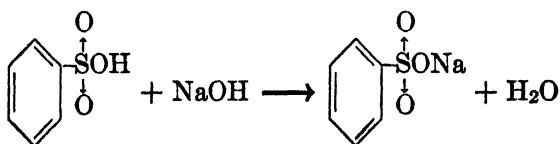
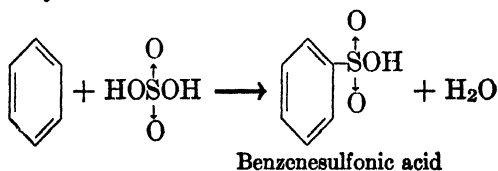
FREDERICK, "Acrylic Resins," *Modern Plastics*, **17** [2], 22 (1939).

## CHAPTER XII

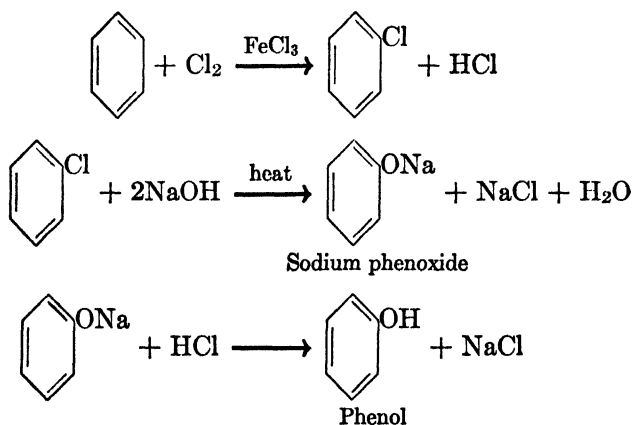
### PHENOLS

The properties of compounds containing a hydroxyl group directly attached to an aromatic ring are altogether different from those of the alcohols. For this reason, these substances constitute a separate class of organic compounds. They are called phenols, after the name of the simplest member.

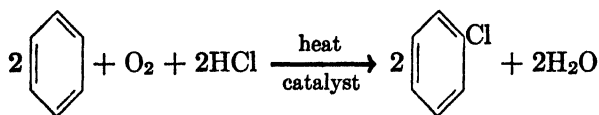
Phenol itself occurs in coal tar, but the supply so available has long been augmented by the commercial synthesis of the substance. The oldest industrial preparation, one which is still in use, is the alkali fusion of sodium benzenesulfonate. The raw materials are benzene, sulfuric acid, and sodium hydroxide.



The more recent methods involve the hydrolysis of chlorobenzene. Aromatic halides are ordinarily very resistant to hydrolysis, and drastic conditions are required to effect the reaction. In one process chlorobenzene is heated under pressure with sodium hydroxide to give sodium phenoxide and sodium chloride. The chlorobenzene may be prepared by chlorination, so the raw materials are benzene, chlorine, and sodium hydroxide.

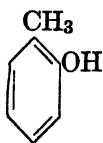


In the newest process, benzene, hydrogen chloride, and air are heated in the presence of a catalyst to form chlorobenzene. Presumably, the oxygen of the air converts the hydrogen chloride to chlorine and the latter attacks the benzene. The hydrogen chloride liberated in the chlorination is reoxidized by the air, so the net reaction can be expressed by the following equation.

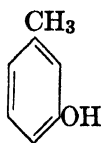


The chlorobenzene is then heated with steam in the presence of a catalyst. Phenol and hydrogen chloride are formed. The hydrogen chloride is returned to the first stage of the process; neglecting any losses of hydrogen chloride, the raw materials are benzene, air, and water.

The cresols and naphthols are important phenols related to toluene and naphthalene, respectively. The cresols are present in coal tar and are obtained by extraction of the middle oil. For most purposes a mixture of the three is used. The naphthols are made by alkali fusion of the corresponding naphthalenesulfonic acids (p. 42). The formulas of the cresols and naphthols are given below.



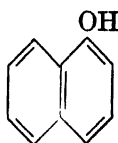
*o*-Cresol  
(m.p. 31°;  
b.p. 191°)



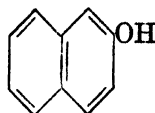
*m*-Cresol  
(m.p. 10°;  
b.p. 203°)



*p*-Cresol  
(m.p. 35°;  
b.p. 201°)

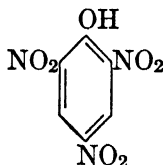


$\alpha$ -Naphthol  
(m.p. 96°)

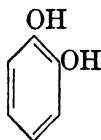


$\beta$ -Naphthol  
(m.p. 122°)

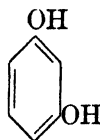
Other phenols of importance in commerce are picric acid (2,4,6-trinitrophenol) and the dihydroxybenzenes, catechol (pyrocatechol), resorcinol, and hydroquinone. The preparations of these compounds are given later. Their structures are as follows:



Picric acid  
(m.p. 122°)



Catechol  
(m.p. 104°)



Resorcinol  
(m.p. 110°)



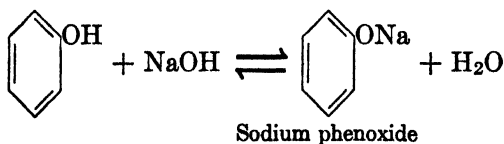
Hydroquinone  
(m.p. 169°)

In the laboratory, phenols are usually prepared by the alkali fusion of sulfonates or by the hydrolysis of diazonium salts (p. 120).

From the melting points (given under the formulas) it can be seen that most of the phenols are solids. Phenol and *o*- and *p*-cresols are often encountered as liquids because a small amount of water, taken up from the air, is sufficient to lower their melting points to values below room temperature.

### Reactions of Phenols

The common name for phenol, "carbolic acid," originates from the fact that phenols are weakly acidic. Most of them are only slightly soluble in water, but they dissolve readily in aqueous sodium hydroxide because of the conversion to salts. The formation of sodium phenoxide is an example.

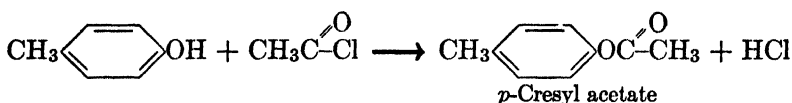


Since the phenols are very weak acids, solutions of their salts are alkaline. Addition of a slightly stronger acid, such as carbon dioxide (carbonic acid), liberates the free phenol. This property can be used in the

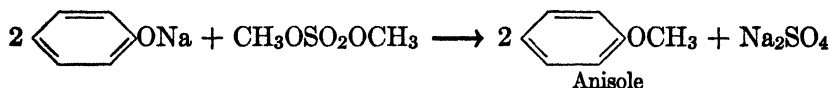
laboratory to distinguish phenols from carboxylic acids, for the latter are not displaced from their salts by carbon dioxide.

Most phenols give highly colored compounds when added to aqueous ferric chloride. This property is often used as a qualitative test for phenols; enols (p. 150) also give colors.

It will be recalled that the alcohols are neutral substances. In the phenols the hydroxyl group is attached to an unsaturated carbon atom, and the compounds are more closely related structurally to the enols (p. 150) than to the alcohols. In most of their chemical properties they show little resemblance to alcohols. For example, they do not react with halogen acids to form halides. In some instances the hydroxyl group of a phenol can be replaced by halogen by treatment with phosphorus halides, but the reaction is of little value in synthesis (p. 244). Phenols cannot be esterified by the direct action of an organic acid, the process most often used in the preparation of esters of alcohols. Esters can be obtained by the action of acyl chlorides or anhydrides on phenols. The preparation of *p*-cresyl acetate is an example.

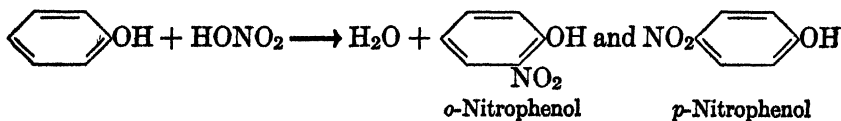


Alkyl ethers of phenols are easily obtained by treating sodium salts of phenols with alkyl halides or alkyl sulfates. For example, anisole is made from sodium phenoxide and methyl sulfate.



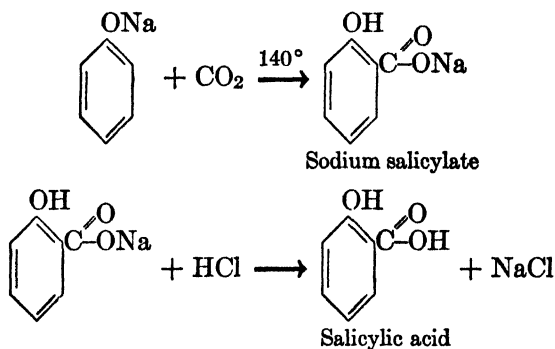
Diaryl ethers can be made from aryl halides and salts of phenols, but, because of the low reactivity of aryl halides, drastic conditions are required.

The properties generally considered most characteristic of phenols, aside from their acidity, are those involving reactions of the aromatic ring. The presence of the hydroxyl group greatly modifies the properties of the ring. In particular, substitution reactions occur with remarkable ease. For example, cold dilute nitric acid (15 per cent) converts phenol to a mixture of *o*- and *p*-nitrophenols, whereas the nitration of benzene requires treatment with a hot mixture of concentrated nitric and sulfuric acids (p. 37).

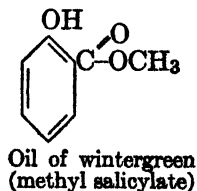
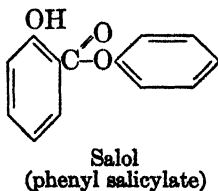
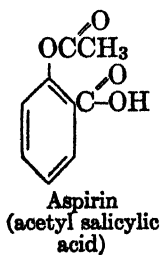


Another example of the enhanced reactivity of the aromatic ring in phenols is the coupling of diazonium salts with these compounds (p. 122). In general, with respect to the ease of substitution the phenols are to be compared to the aromatic amines (p. 232).

When heated with carbon dioxide, the sodium salts of phenols give a peculiar reaction in which a carboxyl group is introduced into the aromatic ring. This is the *Kolbe synthesis*, which is very useful for the preparation of phenolic acids. An example is the synthesis of salicylic acid from sodium phenoxide.

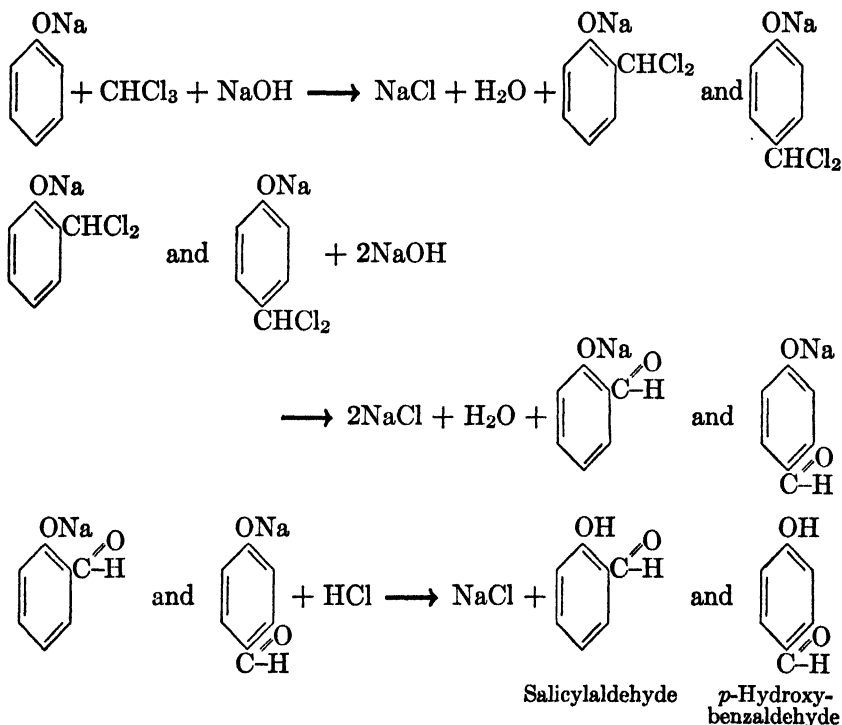


Some *p*-hydroxybenzoic acid also is produced in the reaction. This reaction is carried out on a large scale industrially because of the value of various derivatives of salicylic acid in medicine. The most common of these is aspirin (acetyl salicylic acid), made by treatment of salicylic acid with acetic anhydride. It may be regarded as a substituted phenyl acetate. Aspirin is consumed in the United States at a rate which approximates 5,000,000 lb. per year. Salol is the phenyl ester of salicylic acid. It is used as an intestinal antiseptic. It is made from a mixture of salicylic acid, phenol, and phosphorus oxychloride. Methyl salicylate, known as oil of wintergreen, is applied externally for the relief of rheumatic pains. It is made by the direct esterification of salicylic acid with methyl alcohol. The formulas of these drugs are shown below.





The *Reimer-Tiemann* reaction provides a method for the synthesis of phenolic aldehydes. The sodium (or potassium) salt of a phenol is heated with chloroform in the presence of aqueous alkali to give products containing the aldehyde group in positions *ortho* and *para* to the hydroxyl group. The synthesis of salicylaldehyde and *p*-hydroxybenzaldehyde from sodium phenoxide illustrates the process.

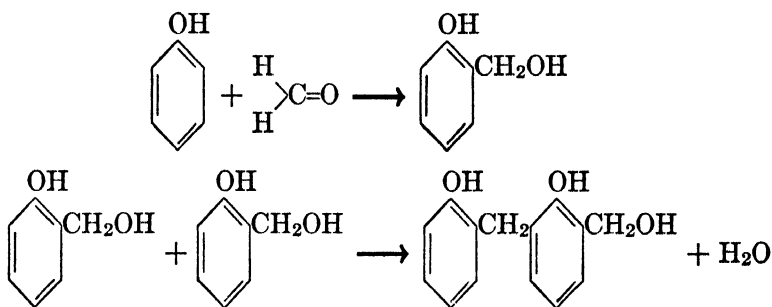


It is believed that the reaction involves the formation of the intermediate dichloro compounds shown in the equations.

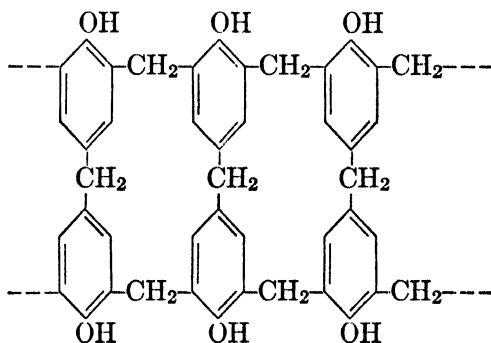
### Industrial Uses of Phenols

The simple phenols are very poisonous and find many uses in the preparation of antiseptics, germicides, and disinfectants. Phenol, the cresols, and resorcinol are present in many such preparations. Phenol is also an important raw material for the manufacture of many dyes and drugs (e.g., the salicylates). The naphthols are extensively used in dye manufacturing. Catechol and hydroquinone are photographic developers. At the present time most of the phenol produced is consumed in the manufacture of synthetic resins. Bakelite, an important

example, is prepared from phenol and formaldehyde in the presence of a trace of ammonia. The reaction proceeds by addition of phenol to formaldehyde and loss of water between the product and another similar molecule. It can be illustrated as follows:



At the same time, reaction occurs in the positions *para* to the hydroxyl group. This leads to the following type of linkage in the final product.



Bakelite is thus a *cross linked, condensation* polymer.

### PROBLEMS

1. Give equations for the conversion of toluene to: (a) *p*-cresol, (b) *p*-cresyl acetate, (c) 2-hydroxy-5-methylbenzaldehyde, (d) ethyl *p*-cresyl ether, (e) 2-hydroxy-5-methylbenzoic acid.

2. Suggest a method for obtaining salicylaldehyde (prepared by the Reimer-Tiemann method) entirely free from phenol.

### SUGGESTED READING

"New Synthetic Phenol Plant," *Ind. Eng. Chem., News Ed.*, 18, 921 (1940).

## CHAPTER XIII

### OPTICAL ISOMERISM

It has been mentioned earlier that lactic acid and certain other hydroxy acids exist in isomeric forms. The fundamental difference between these isomers is in their behavior toward plane polarized light. It is therefore desirable to consider briefly the nature of plane polarized light.

It is a familiar fact that light involves a wave motion. The different colors of light, for example, differ in *wavelength*. The waves which constitute a beam of ordinary light have *all the possible planes of vibration*. This fact can be made clear by reference to Fig. 3, which represents a beam of light traveling toward the eye. It contains waves vibrating in the plane *A*, others vibrating in the plane *B*, and still others vibrating in *all the intermediate planes*.

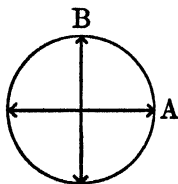


FIG. 3.

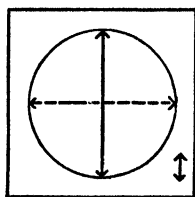


FIG. 4.

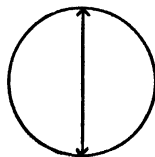


FIG. 5.

A lens made of certain materials, such as tourmaline or Polaroid, has the peculiar property of transmitting only those waves which have planes of vibration in a certain direction called the axis of the lens. Figure 4 shows the effect of such a lens on ordinary light. If the lens is placed in the path of a beam of light with axis of the lens in the vertical position, only those waves which have vibrations in the vertical plane can pass through. The emergent light is plane polarized (Fig. 5). It is possible, then, to define plane polarized light as *light in which all waves vibrate in parallel planes*.

The polarization of light can be proved by a simple experiment using two tourmaline lenses. If these are held between the eye and a light source in positions such that their axes are parallel, then all the light which passes through the first lens also passes through the second, and the latter appears completely transparent (Fig. 6). If one of the lenses is rotated so that its axis is perpendicular to that of the other, then all

the light transmitted by the first lens is absorbed by the second and the latter appears completely opaque (Fig. 7).

The *polarimeter* is an instrument which is used in studying the effect of liquids or solutions on plane polarized light. In its simplest form it consists of a tube, with glass caps, placed between two tourmaline lenses. A light source is placed near one of the lenses, and this lens is held in a fixed position. It is called the polarizer, since it polarizes the light entering the tube. The lens at the other end of the tube is mounted so that it can be rotated.



FIG. 6.

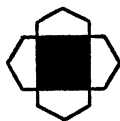


FIG. 7.

It is called the analyzer, because it enables one to determine whether the plane of the polarized light is altered as the light passes through the tube. If the polarizer is arranged with its axis in the vertical position and the polarimeter tube is filled with water, ethyl alcohol, acetone, or ether, it is found that the maximum amount of light passes through the analyzer when its axis is also in the vertical position. This means that the liquids mentioned have no effect on plane polarized light.

However, if the polarimeter tube contains the lactic acid obtained from muscle tissue, it is found that the maximum light transmission

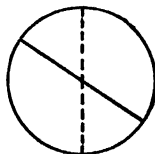
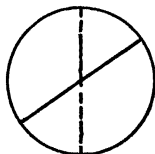


FIG. 8.

by the analyzer occurs when the latter is rotated to the right. This lactic acid must, therefore, rotate the plane of polarized light to the right. It is called *dextro-rotatory* lactic acid. If the tube is now filled with lactic acid obtained by a special fermentation of sugar it will be found to rotate the plane of the light to the left. This lactic acid is called *levo-rotatory* lactic acid. If the two samples are of the same degree of purity and if the amount of rotation by each is measured carefully, it will be found that the number of degrees of rotation to the right effected by the first lactic acid is exactly the same as the rotation to the left caused by the second. Figure 8 shows the results of the above experiment. The dotted line represents the plane of the polarized light entering the liquid and the solid line shows the plane of the light as it leaves the sample.

If a sample of lactic acid prepared by a laboratory synthesis is examined in the polarimeter it is found to have no effect on plane polarized light. This lactic acid is said to be *optically inactive*, in contrast to those

mentioned above which are said to be *optically active*. A careful examination of the properties of the two active acids shows them to be identical in all physical properties, such as melting point, boiling point, solubility, density, *with the single exception of their effect on polarized light*. They also have identical chemical properties. It follows, then, that they have the same structure and that they are equally correctly represented by the formula  $\text{CH}_3\text{CHCO}_2\text{H}$ . However, since there are



two of them, this structure must be capable of existing in two forms.

By the use of tetrahedral atomic models it is indeed found that two models corresponding to the formula  $\text{CH}_3\text{CHCO}_2\text{H}$  can be constructed.



These are shown in Fig. 9. The tetrahedron represents the carbon atom

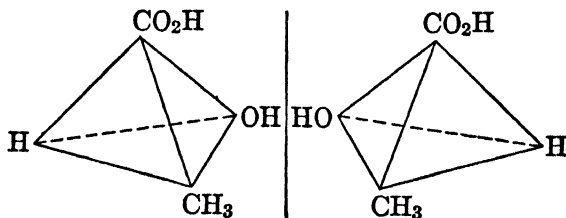


FIG. 9.

marked by an asterisk in the formula just given. These two models bear the same relationship to each other as do the right and left hands. One is the mirror image of the other, but they are not superimposable. They have the same structure, that is, each has a methyl group, a carboxyl group, a hydroxyl group, and a hydrogen atom attached to a carbon atom, but they differ in the order in which these groups are attached, just as the fingers of the left hand may be considered as attached in an order which is the reverse of that of the right hand. The models are said to differ in *configuration*. If one of them is taken to represent dextro-rotatory lactic acid, the other must represent levo-rotatory lactic acid. The two molecules are called *enantiomorphs* or *optical antipodes*.

These models provide a satisfactory explanation for the existence of the two optically active lactic acids. The inactive lactic acid, usually called *racemic* lactic acid, has been found to consist of equal parts of the active acids. Racemic lactic acid is without optical activity because the two active forms exactly neutralize each other.

Lactic acid contains one carbon atom which carries *four different groups*. Such an atom is said to be *asymmetric*. The investigation of a great many substances has shown that those which have one or more

asymmetric carbon atoms are invariably capable of existing in optically active forms. The number of possible optical isomers increases rapidly with the number of asymmetric atoms. It will be instructive to examine a few compounds which have more than one asymmetric atom.

**Two Unlike Asymmetric Carbon Atoms.** Consider the structure

$$\text{CH}_3\overset{*}{\underset{\beta}{\text{CHOH}}}\overset{*}{\underset{\alpha}{\text{CHOH}}}\text{CO}_2\text{H}.$$

The carbon atoms marked with asterisks are asymmetric, and the substituents on the  $\alpha$ -atom are not identical with those on the  $\beta$ -atom. In constructing a model, it would be possible to select the  $\alpha$ -atom in the *d* configuration and add the  $\beta$ -atom in either the *d* or *l* form, or to start with the  $\alpha$ -atom as *l* and add the  $\beta$ -atom in either *d* or *l* configurations. This leads to four forms (Fig. 10).

CO <sub>2</sub> H				
$\alpha$ CHOH	<i>d</i>	<i>d</i>	<i>l</i>	<i>l</i>
$\beta$ CHOH	<i>d'</i>	<i>l'</i>	<i>d'</i>	<i>l'</i>
CH <sub>3</sub>	1	2	3	4

FIG. 10. Two unlike asymmetric carbon atoms.

Forms 2 and 3 will each be optically active since the two asymmetric carbon atoms are unlike and their rotations will not exactly neutralize each other. Forms 1 and 4 are enantiomorphs (mirror images) and will form a racemic modification. Forms 2 and 3 will form a second racemic modification. Form 1 is *not* an enantiomorph of 2 or 3, however. This is an extremely important consideration because optical isomers which are not enantiomorphs have different physical properties and hence can be separated by the usual methods such as crystallization. Optical isomers which are not mirror images are called *diastereoisomers*. If the compound in question were synthesized in the laboratory two products would be obtained. These are the two racemic mixtures (1,4 and 2,3). If the racemic modifications were *resolved* into the active components (p. 170) then four optically active forms would be obtained.

From a similar examination of a compound with three unlike asymmetric carbon atoms it is seen that *eight* active forms are possible. An example is given in Fig. 11.

CO <sub>2</sub> H								
CHOH	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>l</i>	<i>l</i>	<i>l</i>	<i>l</i>
CHOH	<i>d'</i>	<i>d'</i>	<i>l'</i>	<i>l'</i>	<i>d'</i>	<i>d'</i>	<i>l'</i>	<i>l'</i>
CHOH	<i>d''</i>	<i>l''</i>	<i>d''</i>	<i>l''</i>	<i>d''</i>	<i>l''</i>	<i>d''</i>	<i>l''</i>
CH <sub>3</sub>	1	2	3	4	5	6	7	8

FIG. 11. Three unlike asymmetric carbon atoms.

It will be noted that in this case four racemic modifications are possible (1,8; 2,7; 3,6; 4,5). A laboratory synthesis would yield these four racemic forms and separation of each would give the eight active forms.

From the three examples considered it is evident that the addition of a new, different asymmetric carbon doubles the number of active forms. The number of active forms can be predicted from the equation below, in which  $n$  represents the number of unlike asymmetric carbon atoms.

$$\text{Number of active forms} = 2^n$$

**Two Similar Asymmetric Carbon Atoms.** Tartaric acid presents an interesting case, since it has two asymmetric carbon atoms which have identical groups attached. If the two possibilities for each carbon atom are considered as was done above, the forms 1,2,3, and 4 (Fig. 12) might be written. However, when it is remembered that the asymmetric carbon atoms are alike it will be seen that forms 2 and 3 are identical. Moreover, the form in

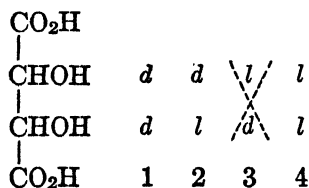


FIG. 12.

which the two identical asymmetric atoms have opposite configurations will be optically inactive. The dextro-rotatory effect of the one atom will be exactly neutralized by the levo-rotatory effect of the other. This is not a racemic form since the neutralization is *within* the molecule, whereas in a racemic form neutralization occurs *between* molecules. The internally neutralized isomer is said to be a *meso* form. Thus there are three individual tartaric acids, dextro-rotatory tartaric, levo-rotatory tartaric, and meso-tartaric acids. Racemic tartaric acid is, of course, a mixture of the two active forms.

**Projection Formulas.** It is possible to represent the various optical isomers with plane formulas by the aid of certain conventions. Consider the models of the two lactic acids (Fig. 13). If it is agreed that in writing plane formulas of the lactic acids the carboxyl group shall always be placed at the top of the formula and the methyl group at the bottom, then the difference between the two isomers can be shown by the formulas below the models.

These plane formulas are called projection formulas; they may be regarded as the shadows cast by the three-dimensional models. With their aid it is possible to represent on paper even very complicated cases of optical isomerism. They must be used by the beginner with caution and with frequent reference to the three-dimensional models, however. For instance, a student occasionally inquires how the two projection formulas of the lactic acids can be different when he can make them coin-

cide by folding the paper between them. If he keeps in mind the three-dimensional models just above the formulas, he will see that the two models do not coincide during this operation.

It has been found that many of the derivatives of *dextro-rotatory* lactic acid are *levo-rotatory*. If the acid is dissolved in water and neutralized with a metallic hydroxide, for example, the rotation changes from a plus value to a minus value. If an equivalent amount of a mineral acid is now added to regenerate the acid the rotation changes in the reverse

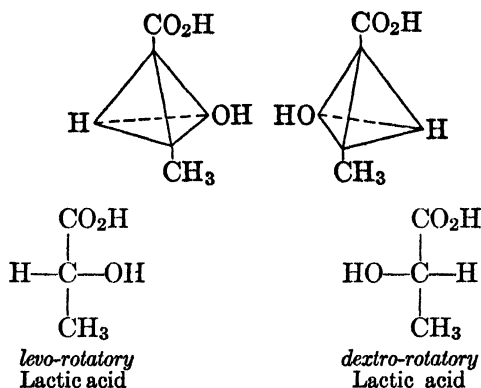
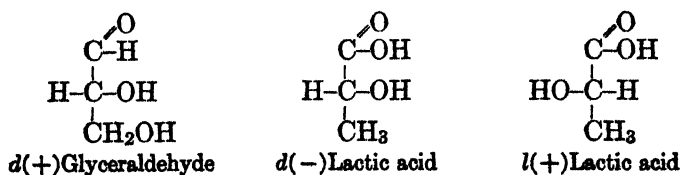
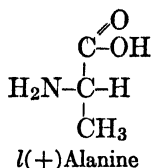
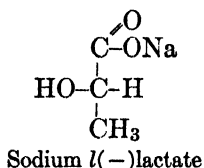


FIG. 13.

manner. It is desirable to have some notation to show that these *levo-rotatory* salts are related to the *dextro-rotatory* acid. This has been done by making *dextro-rotatory* glyceraldehyde the standard of reference. It was agreed that the *dextro configuration*, for any carbon atom, shall be defined as that corresponding to the configuration of the asymmetric carbon atom in *dextro-rotatory* glyceraldehyde. An enantiomorph in which the asymmetric carbon atom has this configuration shall be considered as a member of the *dextro* series, regardless of the direction of its rotation. When desired, the rotation is specified by including in the name a plus sign or a minus sign. *Dextro-rotatory* glyceraldehyde has been found to be related to *levo-rotatory* lactic acid. This lactic acid is therefore written as *d*(-)*lactic acid*. Other examples of this very convenient system are shown in the projection formulas and names below.







In each case the letter indicates the *absolute configuration* of the asymmetric carbon atom and the sign indicates the direction of rotation of the compound. This notation has been extended to apply to compounds with many asymmetric carbon atoms (p. 187). Unfortunately, it has been adopted only recently, so that in the use of the chemical literature one must determine for each author whether the expression *d* isomer is used to indicate absolute configuration or direction of rotation.

**Resolution of Racemic Modifications.** There are three general methods of separating a racemic modification into its active components. They are the mechanical, the biological, and the chemical methods.

**Mechanical Resolution.** Occasionally the two substances which constitute a racemic modification crystallize separately. If the two types of crystals can be distinguished from each other they can be separated with the aid of a magnifying glass. The first resolution was accomplished by Pasteur in this manner. The method has the disadvantage that it is rarely applicable, and when it can be used it is extremely tedious.

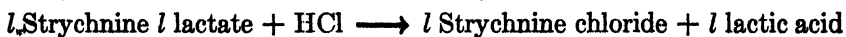
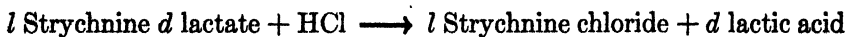
**Biological Resolution.** If the racemic substance is acted upon by a bacterium, a yeast, or a mold, one of the active forms will be utilized more rapidly than the other. Often one form is completely unaffected. The difficulties with this method are that it may not be easy to find the appropriate biological agent, the resolution may be incomplete, and at best only one of the two active forms can be obtained.

**Chemical Method.** The most satisfactory method of resolution consists in treating the racemic compound with an optically active reagent. Two diastereoisomeric products are formed. These are separated and purified by recrystallization, and each is treated with a reagent which will regenerate the starting material. The resolution of lactic acid by the aid of *l* strychnine is an example.

*dl* Lactic acid + *l* Strychnine



The two *l* strychnine lactates are not mirror images and they can be separated because of their different solubilities. Each salt is purified and treated with hydrochloric acid.



Because naturally occurring compounds are nearly always produced in optically active forms, if optical activity is possible, a large number of active acids, bases, alcohols, etc., are available as resolving agents.

The role of optically active compounds in physiological chemistry is of great interest. Not only do plants and animals usually synthesize compounds which have asymmetric carbon atoms as the individual active forms, but also often only one of the active forms is utilized in metabolic processes. The pronounced effect of many substances, such as vitamins and hormones, is often characteristic of only one of the optical isomers. Such differences in physiological effects can be explained on the assumption that the substances act on the body by combining with some optically active compound already present. In this way the "natural" and "unnatural" enantiomorphs would yield two diastereoisomers which would have different physical properties and hence different physiological effects.

It is not nearly so easy to understand how optically active forms are synthesized in nature. An idea of the problem here can be gained from

a consideration of the reduction of pyruvic acid ( $\text{CH}_3\text{C}(=\text{O})\text{COOH}$ ) to lactic acid. In Fig. 14 the ketone carbon atom is represented by the tetrahedron.

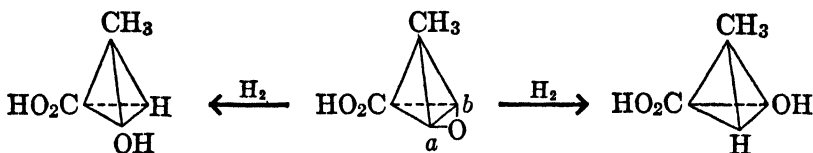


FIG. 14.

The two bonds *a* and *b* which connect the carbon and oxygen atoms are identical. If the reduction is carried out in the laboratory these two bonds are broken at exactly the same rate, and the product is racemic lactic acid. However, if the reaction occurs as part of a biological process, then it will take only one of the two possible courses and the product will be an active lactic acid. No completely satisfactory theory of the specificity of such reactions in nature has yet been advanced.

The optical rotation of a natural substance is often of great value in identification and analytical work. In order to measure it accurately, very sensitive polarimeters have been devised. Because the actual rotation of a substance varies with the solvent, the concentration, the length of the column of substance through which the polarized light passes, the temperature, and the wavelength of light employed, the

results are usually calculated to "specific rotations" by the aid of one of the following formulas.

$$\text{For pure liquids } [\alpha]_D^{25} = \frac{a}{ld}$$

$$\text{For solutions } [\alpha]_D^{25} = \frac{100a}{lc}$$

$a$  = observed rotation at  $25^\circ$ .

$l$  = length of polarimeter tube expressed in decimeters.

$d$  = density.

$c$  = concentration (grams per 100 cc. of solution).

$[\alpha]_D^{25}$  = specific rotation at  $25^\circ$  with respect to light of a sodium lamp (D line of sodium spectrum).

When the second equation is used the solvent and concentration must be reported along with the calculated rotation. For example, the specific rotation of  $l(+)$ tartaric acid is recorded as " $+11.98^\circ$  in 20 per cent aqueous solution."

### PROBLEMS

1. Define and illustrate the following terms: (a) plane polarized light, (b) asymmetric carbon atom, (c) dextro-rotatory form, (d) configuration, (e)  $d$  configuration, (f) racemic form, (g) *meso* form, (h) enantiomorphs, (i) diastereoisomers, (j) resolution.

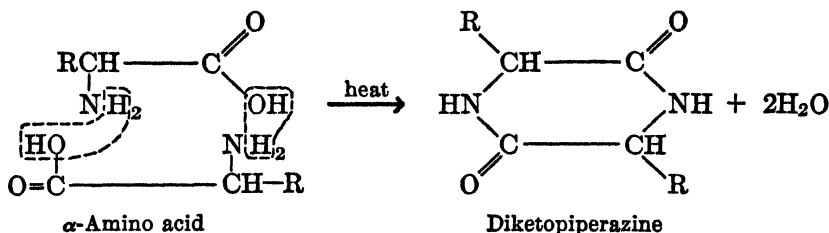
2. Predict the number of optically active forms of: (a)  $\alpha$ -amino- $n$ -caproic acid, (b) 1,2-butanediol, (c) 2,3-butanediol, (d)  $\alpha$ -amino- $\beta$ -hydroxybutyric acid, (e) 2,3,4-trimethylhexane.

## CHAPTER XIV

### AMINO ACIDS AND PROTEINS

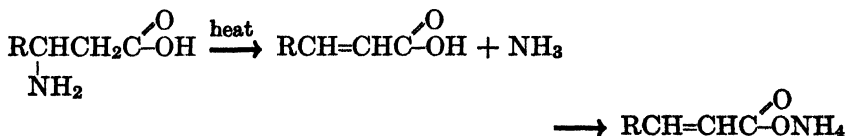
Compounds containing both a carboxyl group and an amino group are known as amino acids. They are usually classified as  $\alpha$ -,  $\beta$ -,  $\gamma$ -, etc., amino acids, depending on the distance between the two functional groups. Each type has, in general, the properties of the amines as well as those of the acids. Each type also has certain special properties, depending on the influence of the two functional groups on each other. Only these special properties are discussed in this chapter.

The behavior of the amino acids on heating closely parallels that of the hydroxy acids (p. 142). For example,  $\alpha$ -amino acids lose water to form diketopiperazines, compounds which may be regarded as the nitrogen analogs of the lactides (p. 142).

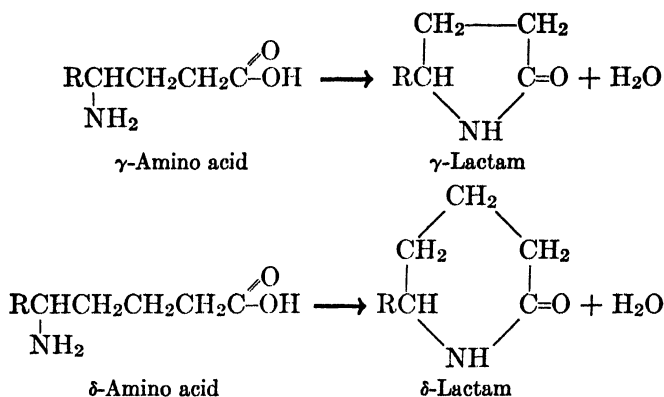


In practice, the diketopiperazines are best obtained from esters of  $\alpha$ -amino acids.

$\beta$ -Amino acids decompose on heating to form ammonia and an unsaturated acid. The reaction resembles the dehydration of  $\beta$ -hydroxy acids.



$\gamma$ - and  $\delta$ -Amino acids lose water to form cyclic amides known as lactams. Their formation recalls the production of lactones from hydroxy acids (p. 144).

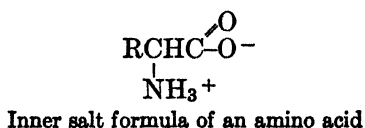


### The Proteins

The proteins are organic materials which are present in all living organisms. In the plants, only the seeds contain appreciable quantities of proteins. Animals, however, are constructed largely of proteins. Hair, nails, feathers, horns, hoofs, skin, muscles, tendons, and nerve tissues are essentially proteins. The albumen of egg-white, the casein of milk, and the hemoglobin of the blood are examples of individual proteins.

The properties of proteins show them to be polymeric. The molecular weights have been estimated to vary from 17,500 for lactalbumin (from milk) to as high as 50,000,000 for the tobacco mosaic protein (p. 359). Knowledge of the structure of these extremely complex compounds has been gained largely by the study of their hydrolysis products. All proteins are converted to mixtures of  $\alpha$ -amino acids by hydrolysis. Examination of the hydrolysis products of a great variety of proteins has revealed the presence of only twenty-four different  $\alpha$ -amino acids. Their names and formulas are given in Table XXIV. It is possible that other  $\alpha$ -amino acids may also be involved in proteins. Several which do not appear in the table have been isolated from natural sources, but they have not been shown to occur generally as products of protein hydrolysis.

The natural amino acids fall into three groups, the neutral amino acids, the acidic amino acids, and the basic amino acids (Groups I, II, and III of Table XXIV). Of the neutral compounds all but tryptophan possess one amino group for each carboxyl group. These compounds actually have many of the properties of salts and are, perhaps, better represented by the inner salt ("zwitterion") formula as follows:



Tryptophan, although it has two amino groups, is classed as a neutral amino acid because the secondary amino group is attached to two unsaturated carbon atoms and hence is practically neutral (compare with diphenylamine, p. 391). The members of the second class have two carboxyl groups for each amino group. Those of the last type have a preponderance of basic groups.

It will be noted that each of the natural amino acids, except glycine, has at least one asymmetric carbon atom and is, therefore, capable of existing as optical isomers. Careful hydrolysis of proteins invariably yields optically active amino acids, never racemic modifications. It is a striking fact that the  $\alpha$ -carbon atoms of all these active forms have the same (*l*) configuration (p. 166).

When a protein is ingested it is hydrolyzed in the digestive tract to the component amino acids. It has been found that dietary protein can be replaced by mixtures of pure amino acids. Only nine of the twenty-four known amino acids are necessary to support growth in young animals. If any one of these nine is absent from the diet the animal fails to grow and may even die. These nine are called essential amino acids; they are marked with asterisks in Table XXIV. The protein of an animal fed only the nine essential amino acids is found to contain many of the others. This means that the animal body is capable of synthesizing some of the amino acids and the nine essential ones are those which cannot be synthesized in the animal and so must be obtained from external sources, ultimately plants. Another curious fact is that some of the essential amino acids are utilized in either form (*d* or *l* configuration of the  $\alpha$ -carbon atom) but others must be supplied in the natural (*l*) configuration. This indicates that, in some cases, the animal can convert one optical isomer into its enantiomorph.

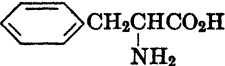
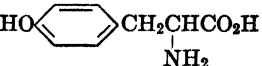
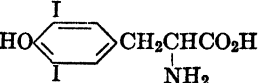
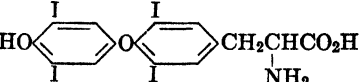
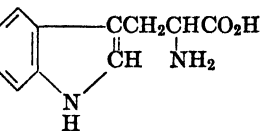
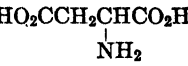
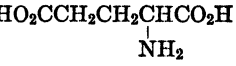
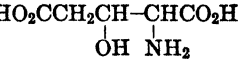
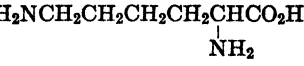
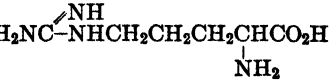
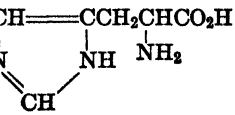
Thyroxine occupies a unique place among amino acids. It is found only in the hydrolysis products of the hormone thyroglobulin, a protein produced by the thyroid gland. Hormones are substances secreted internally by the endocrine (ductless) glands and carried by the blood or lymph to other portions of the body, the functions or structures of which are thereby altered. The thyroid hormone is a protein in which thyroxine and a number of other amino acids are combined. The activity of the hormone is due to the thyroxine present in the protein. Thyroxine contains a high percentage of iodine, and in regions where the water is deficient in this element the diet of the inhabitants may be so low in iodine that insufficient thyroxine is produced by the thyroid gland. This leads to various disorders of which endemic goiter is the best known. Extracts of thyroid glands obtained from slaughtered cattle are used in treating such disorders, as is also pure synthetic thyroxine.

TABLE XXIV  
NATURAL AMINO ACIDS

Name	Formula
I <i>Neutral amino acids</i>	
Glycine	$\text{H}_2\text{NCH}_2\text{CO}_2\text{H}$
Alanine	$\begin{array}{c} \text{CH}_3\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Valine *	$\begin{array}{c} \text{CH}_3\text{CH}-\text{CHCO}_2\text{H} \\   \quad   \\ \text{CH}_3 \text{NH}_2 \end{array}$
Leucine *	$\begin{array}{c} \text{CH}_3\text{CHCH}_2\text{CHCO}_2\text{H} \\   \quad   \\ \text{CH}_3 \text{NH}_2 \end{array}$
Norleucine	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Isoleucine *	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}-\text{CHCO}_2\text{H} \\   \quad   \\ \text{CH}_3 \text{NH}_2 \end{array}$
Serine	$\begin{array}{c} \text{HOCH}_2\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Threonine *	$\begin{array}{c} \text{CH}_3\text{CH}-\text{CHCO}_2\text{H} \\   \quad   \\ \text{OH} \text{NH}_2 \end{array}$
Cysteine	$\begin{array}{c} \text{HSCH}_2\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Cystine	$\begin{array}{c} \text{S}-\text{CH}_2\text{CHCO}_2\text{H} \\   \quad   \\ \text{S}-\text{CH}_2\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Methionine *	$\begin{array}{c} \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCO}_2\text{H} \\   \\ \text{NH}_2 \end{array}$
Proline	$\begin{array}{c} \text{CH}_2-\text{CH}_2 \\   \quad   \\ \text{CH}_2 \quad \text{CHCO}_2\text{H} \\ \diagdown \quad \diagup \\ \text{NH} \end{array}$
Hydroxyproline	$\begin{array}{c} \text{HOCH}-\text{CH}_2 \\   \quad   \\ \text{CH}_2 \quad \text{CHCO}_2\text{H} \\ \diagdown \quad \diagup \\ \text{NH} \end{array}$

\* Essential amino acid (p. 175).

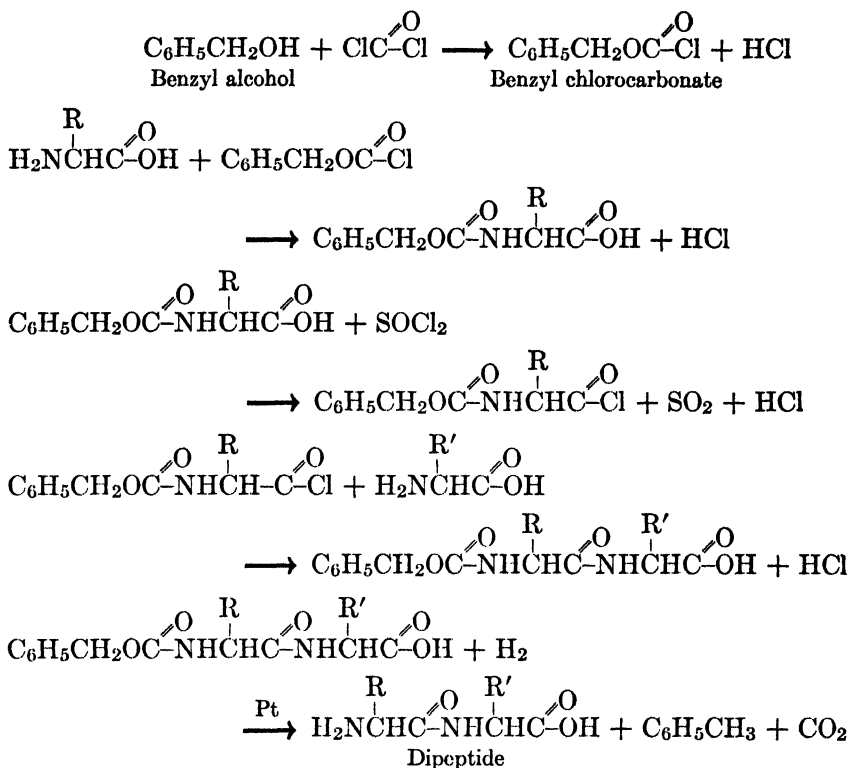
TABLE XXIV (Continued)

Name	Formula
<b>I Neutral amino acids (Continued)</b>	
Phenylalanine *	
Tyrosine	
Diiodotyrosine	
Thyroxine	
Tryptophan *	
<b>II Acidic amino acids</b>	
Aspartic acid	
Glutamic acid	
Hydroxyglutamic acid	
<b>III Basic amino acids</b>	
Lysine *	
Arginine	
Histidine *	

\* Essential amino acid (p. 175).







If a tripeptide were desired the last intermediate could be converted to the acid chloride and condensed with another molecule of amino acid. By this and similar methods polypeptides of molecular weight above 1000 have been prepared. These synthetic polypeptides have some of the properties of proteins, but the highest molecular weight so far attained is only a fraction of that of the smallest protein.

The amphoteric character of most proteins results from the presence of both acidic and basic amino acid units in the protein molecule. A protein composed exclusively of neutral amino acids would have but one free amino group and one free carboxylic group, at either end of the chain, and these could hardly be expected to exert an appreciable influence on so large a molecule. However if units of acidic and basic amino acids are scattered at various points along the chain, then the molecule will have a number of free acid and basic groups and will be amphoteric. Some proteins have the power to react with more equivalents of base than of acid, whereas others consume a larger amount of acid than of base. Examination of the hydrolysis products of a protein of the former type reveals a preponderance of acidic amino acids as compared with the

basic amino acids, whereas the reverse is true of the hydrolysis products of proteins of the second group.

The presence of charged groups at points along a protein chain also may have an important influence in causing the chains to associate. Some such association may account for the enormous molecular weights of certain proteins. For example, physical measurements which indicated the molecular weight of a sample of a protein (hemocyanin) to be 6,740,000 gave values which were successively one-half, one-eighth, and one-sixteenth of this figure as the acidity of the solution was changed. By restoring the acidity to its original value the initial molecular weight was again indicated. With certain other proteins the apparent molecular weight has been found to be affected by the concentration of salt in the aqueous solution of the protein.

It was mentioned above that ingested protein is hydrolyzed to the constituent amino acids during digestion. The hydrolysis is brought about by the proteolytic enzymes of the stomach and intestine. The individual amino acids pass through the intestinal wall into the blood stream, and some of them are combined in the various body proteins. If the foreign protein or its partial hydrolysis products, known as proteoses and peptones, find their way into the blood stream they act as violent poisons. Idiosyncrasies of individuals to certain foods are believed due to permeability of the intestinal wall to proteins of the food. The allergies, such as asthma and hay fever, are ascribed to conditions in which foreign protein enters the body. The venoms of certain reptiles are proteins which are poisonous because they are injected into the blood stream without preliminary hydrolysis. Serum sickness is caused by traces of protein carried over from the animal from which the serum was taken.

The above facts indicate that each protein has its own individuality; similar proteins taken from different species are not identical. This has been demonstrated chemically in the case of hemoglobins from various animals. By hydrolyzing weighed samples of proteins and analyzing the hydrolysate it is possible to determine quite accurately the amounts of some of the amino acids. From the analytical result the ratios of these amino acids in the protein can be calculated. When this was done with hemoglobin from the horse, the sheep, the cow, and the dog, it was found that arginine, histidine, and lysine were present in the ratio 12 to 32 to 36. However, the figure for cysteine was 2 for horse hemoglobin, 3 for sheep and cattle hemoglobins, and 4 for dog hemoglobin. This demonstrates a definite difference in the amino acid make-up of the hemoglobin of either the horse or dog as compared to that of the cow and sheep. It is also possible that they differ in the order in which the amino acid units are

joined together, much as words differ in the order in which their letters are grouped. If this possibility is admitted there is no limit to the number of proteins which may exist.

It can be concluded that present knowledge of the structures of proteins indicates that they are polypeptides, but that much remains to be learned about the detailed arrangements within the giant molecules.

**Classification of Proteins.** Proteins which give only  $\alpha$ -amino acids upon hydrolysis are known as simple proteins. These are further classified as albumins, globulins, glutelins, and others on the basis of their solubilities in various salt solutions and acidic or basic solutions. Conjugated proteins yield on hydrolysis  $\alpha$ -amino acids plus some other compound which may be a pigment (such as hemin from hemoglobin), a sugar, a derivative of phosphoric acid, or other substance. The products obtained from proteins by the action of heat and the chemical reagents mentioned in the next paragraph are known as derived proteins.

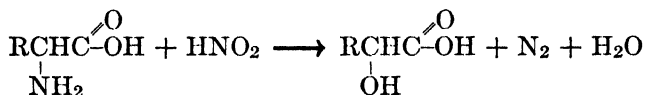
**Coagulation and Precipitation of Proteins.** An important property of soluble proteins is their tendency to form insoluble precipitates, known as *coagulated proteins*, under the influence of heat, ultraviolet light, or alcohol. The hardening of egg albumen and casein on heating are facts familiar to everyone. The mild action of acids or bases on proteins brings about a less profound change. The products are said to be *denatured proteins*; they do not dissolve in neutral solutions but are soluble in acids and bases. Certain heavy metal salts and tannic acid convert proteins into insoluble compounds. The poisonous nature of salts of mercury, lead, and silver has been attributed to the conversion of body proteins into insoluble compounds. In the preparation of *leather*, chromic salts and tannic acid are employed to change the protein of the skin into insoluble materials. Formaldehyde converts soluble proteins into tough, hard, insoluble materials. Such products from casein and formaldehyde have long been used as substitutes for ivory, horn, and hard rubber, and for waterproofing of paper and textiles. In some countries artificial wool is prepared from casein and formaldehyde. It is possible to use other soluble proteins, such as that from soybean, in similar applications.

**Tests for Proteins.** Many color reactions are characteristic of proteins and are used in testing for their presence. Biuret (p. 128) gives a violet color in the presence of dilute sodium hydroxide and a copper salt. Other

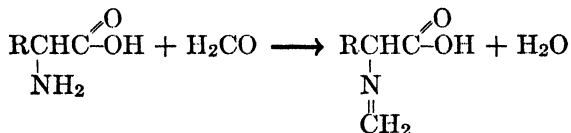
substances containing two or more  $\begin{array}{c} \diagup \text{O} \\ \text{—C—NH} \\ | \end{array}$  links, notably the proteins, yield similar colors. The test is known as the biuret test but its widest application is in connection with proteins, as, for instance, in determining when the hydrolysis of a protein has proceeded to a stage where only  $\alpha$ -amino acids are present. Proteins which contain amino acid units

with aromatic groups give a yellow color with nitric acid. The coloring of the skin by nitric acid is familiar to every chemist. This test is known as the xanthoproteic test. Many proteins contain one or more of the sulfur-containing amino acids and hence give a black precipitate (lead sulfide) when heated with a solution of a lead salt.

The most useful quantitative analyses in connection with proteins are the determination of total nitrogen, usually by the Kjeldahl method, and the determination of amino nitrogen in amino acid mixtures, such as protein hydrolysates, by the Van Slyke method. This consists in bringing the sample in contact with nitrous acid and measuring the volume of nitrogen gas produced. The reaction is that of a primary amine with nitrous acid (p. 118), as shown by the following equation.

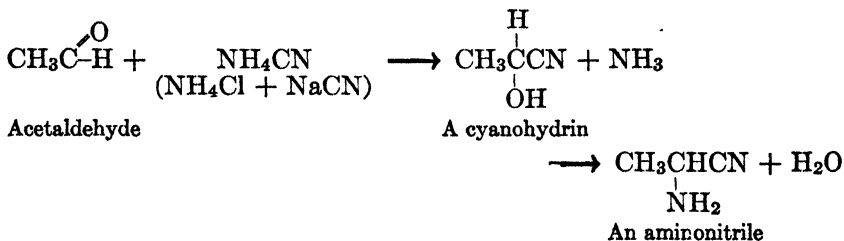


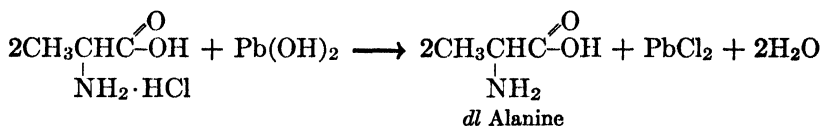
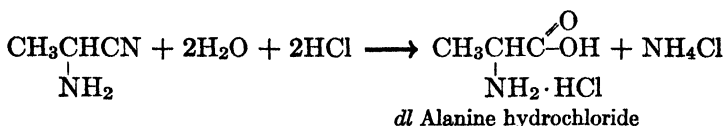
Amino acids are sometimes titrated after treatment with formaldehyde. The formaldehyde destroys the basicity of the amino group, so that the carboxyl group is easily titrated. The reaction may be that shown in the following equation.



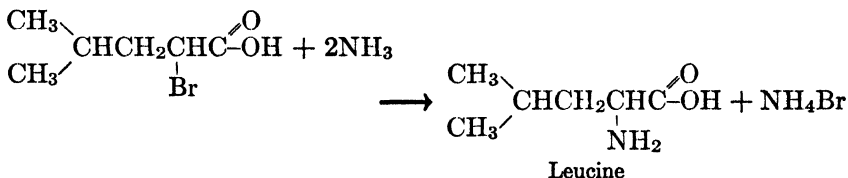
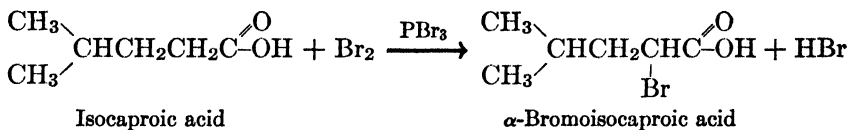
### The Synthesis of Amino Acids

From the foregoing discussion it will be realized that great interest attaches to methods of synthesis of  $\alpha$ -amino acids. A number of processes have been developed, and only a few of them can be described here. One very useful method is the Strecker synthesis of an amino acid from an aldehyde with one less carbon atom. When an aldehyde is treated with ammonium cyanide it forms the cyanohydrin and ammonia. These react to give the amino nitrile, which is then hydrolyzed to the amino acid. The synthesis of *dl* alanine serves as an example.

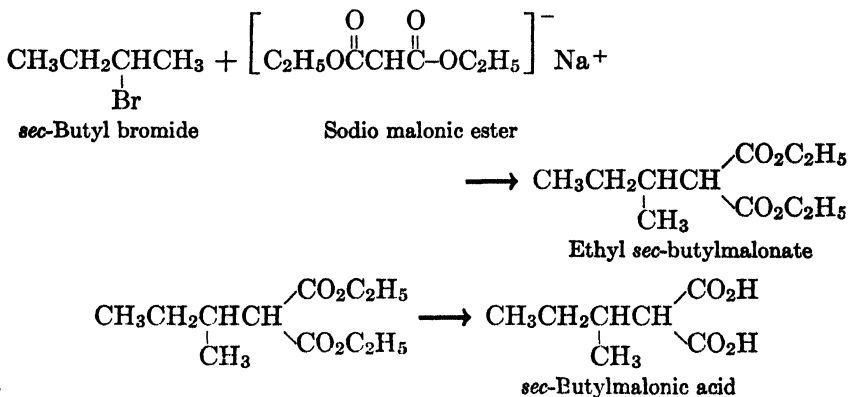


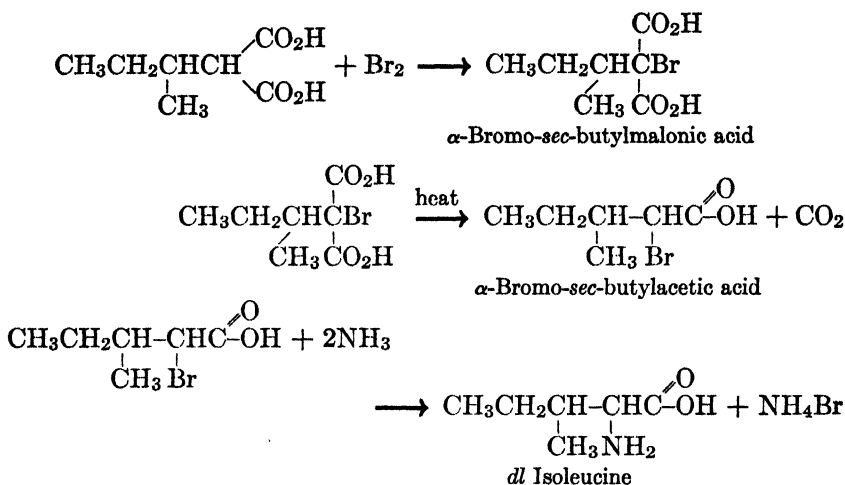


Another method involves the reaction of an  $\alpha$ -bromo acid with ammonia. Sometimes the  $\alpha$ -bromo acid can be obtained by direct bromination of the acid (Hell-Volhard-Zelinsky bromination, p. 236) as in the synthesis of *dl* leucine. The isocaproic acid required in this preparation is made from isoamyl alcohol (p. 54). The equations for the reactions are given below.

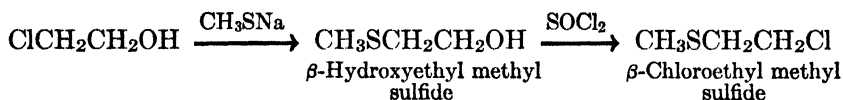


If the acid used in the synthesis is prepared by the malonic ester method, the substituted malonic acid is sometimes brominated before decarboxylation. This is done in the synthesis of *dl* isoleucine, which is made from *sec*-butyl bromide by the following reactions.

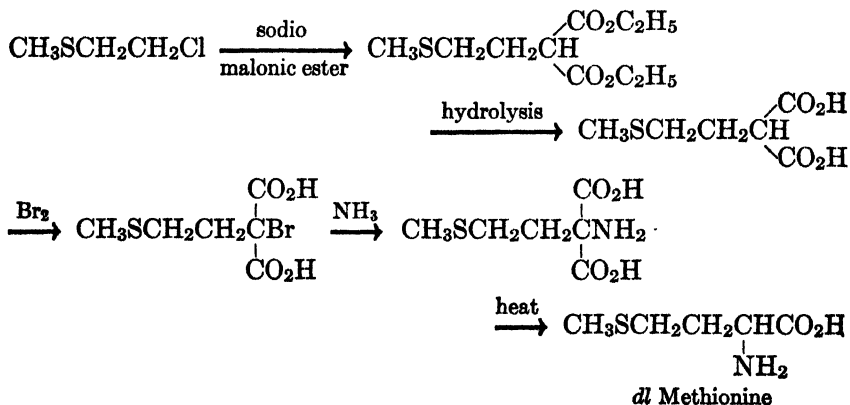




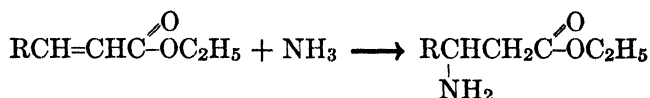
When the malonic ester method is used it is also possible to aminate the bromomalonic acid prior to decarboxylation. One synthesis of *dl* methionine is run in this way. The desired malonic acid is made from malonic ester and  $\beta$ -chloroethyl methyl sulfide prepared from ethylene chlorohydrin by the following scheme.



The  $\beta$ -chloroethyl methyl sulfide is condensed with malonic ester and the substituted malonic acid is obtained by hydrolysis. This is converted to the bromomalonic acid, then to the aminomalonic acid, and finally to *dl* methionine. The reactions are represented by the following scheme.

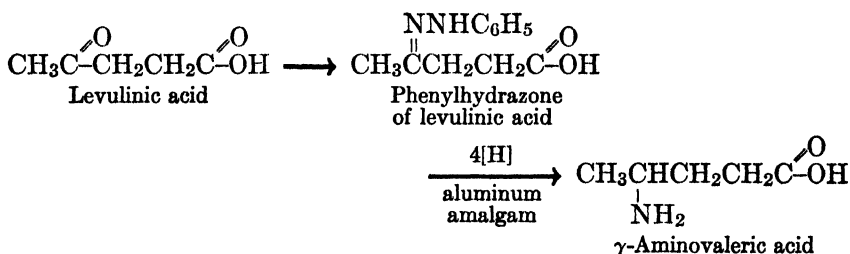


$\beta$ -Amino acids are most conveniently prepared by addition of ammonia to  $\alpha, \beta$ -unsaturated esters. This is an example of 1,4 addition (p. 26). The process is illustrated by the general equation below.



The acid is obtained by hydrolysis of the ester.

There are no general methods for the preparation of  $\gamma$ - and  $\delta$ -amino acids. When the corresponding keto acids are available they can be converted to the amino acids by reduction of the phenylhydrazones.  $\gamma$ -Aminovaleric acid is made from levulinic acid by this method.



Aromatic amino acids having an amino group attached to the aromatic ring are often prepared by reduction of the nitro acids. The synthesis of *p*-aminobenzoic acid (p. 384) is an example.

## PROBLEMS

1. Define and illustrate the following: (a) dipeptide, (b) polypeptide, (c) neutral amino acid, (d) basic amino acid, (e) simple protein, (f) derived protein, (g) essential amino acid.
2. Give equations for the preparation of *dl* norleucine by means of (a) the Strecker synthesis, (b) the malonic ester synthesis, (c) another method.
3. Write the formula of a neutral tripeptide, of a basic tripeptide, of an acidic tripeptide. Explain why soluble proteins are amphoteric.



## CHAPTER XV

### CARBOHYDRATES

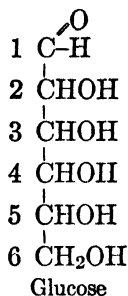
Plants are composed largely of organic materials called carbohydrates. It has been mentioned that seeds of plants contain proteins and fats, sometimes in rather large amounts. The substances which constitute other parts of plants, the roots, stems, leaves, bark, etc., are almost wholly carbohydrate. The name derives from the formulas of the first of these materials to be examined, which could be written as  $C_mH_{2n}O_n$  or  $C_m(H_2O)_n$  and were therefore thought to be hydrates of carbon. This supposition proved to be false, for the compounds are not hydrates and many of them do not even correspond to these general formulas. The name carbohydrate has been retained, nevertheless; a modern definition is given later (p. 195).

The carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides. It is convenient to begin the discussion with the simplest members, the monosaccharides.

#### Monosaccharides

**Glucose**, also known as dextrose or corn sugar, is the commonest of the monosaccharides. It has the formula  $C_6H_{12}O_6$ . It is an optically active, neutral, solid substance, extremely soluble in water. It is oxidized by copper or silver oxides (p. 68) to an acid of the formula  $C_6H_{12}O_7$ . This shows that glucose is an aldehyde. When glucose is treated with acetic anhydride it yields an ester whose formula  $[C_{16}H_{22}O_{11}]$  or  $C_6H_7O(OCOCH_3)_5$  shows it to be a pentaacetate. Thus glucose must be a pentahydroxyaldehyde. Since the substance is not easily dehydrated no two of the hydroxyl groups can be attached to the same carbon atom (p. 299), and it can be said that of the six carbon atoms in the molecule, one is part of a carbonyl (aldehyde) group and the other five each carry one hydroxyl group. The question remaining, then, is whether the six carbon atoms form a straight or branched chain. Since glucose is reduced by phosphorus and hydrogen iodide to a mixture of

*straight-chain* iodohexanes, the carbon atoms must be in a straight chain. The formula of glucose can then be written as follows.



In this formula there are four unlike asymmetric carbon atoms, so it should represent  $2^4$  or 16 different optical isomers. These are all known; they fall into eight pairs of enantiomorphs. The configuration of each carbon atom in glucose and its optical isomers is known. By the use of the conventions developed for representing optically isomeric substances with projection formulas (p. 168), it is possible to show the differences between these isomers, and this is done below (Fig. 15). It will be recalled that the configuration of an asymmetric carbon atom is assigned on the basis of its relationship to the asymmetric carbon atom in *d*(+)-glycerose, and not on the basis of the rotation of the compound in question (p. 169). In order to have a system of naming enantiomorphous pairs in the sugar series it has been agreed that the asymmetric carbon atom nearest the primary hydroxyl group, that is, carbon atom number 5 in the usual scheme of numbering the atoms in the carbon chains of the sugars, shall be taken as the point of reference. Of each pair of enantiomorphs, that one in which carbon atom number 5 has the same configuration as the asymmetric atom of *d*(+) glycerose shall be referred to as the *d* isomer, regardless of its optical rotation. This system is illustrated in Fig. 15. The formulas of only the *d* compounds are given. The projection formula of any of the *l* isomers can be written by reversing the positions of the hydrogen atom and the hydroxyl group on each asymmetric carbon atom of the corresponding *d* isomer.

The six-carbon atom monosaccharides are called hexoses. Monosaccharides containing the aldehyde group are known as aldoses. It is convenient to combine the two names and to designate glucose and its optical isomers as the aldohexoses.

As indicated in Fig. 15, the correct designation of ordinary glucose is *d*(+)-glucose. Since *l*(-)-glucose does not occur in natural products

many writers use only the word glucose for the ordinary material. Others employ the terms *d* glucose and *D*-glucose. In the sequel the letters *d* and *l* will be used to denote configuration only; when it is desired to indicate direction of rotation, the plus or minus sign will be used.

The fact that reactions of *d*(+)-glucose often lead to mixtures of two isomeric products may well have been distressing to early carbohydrate

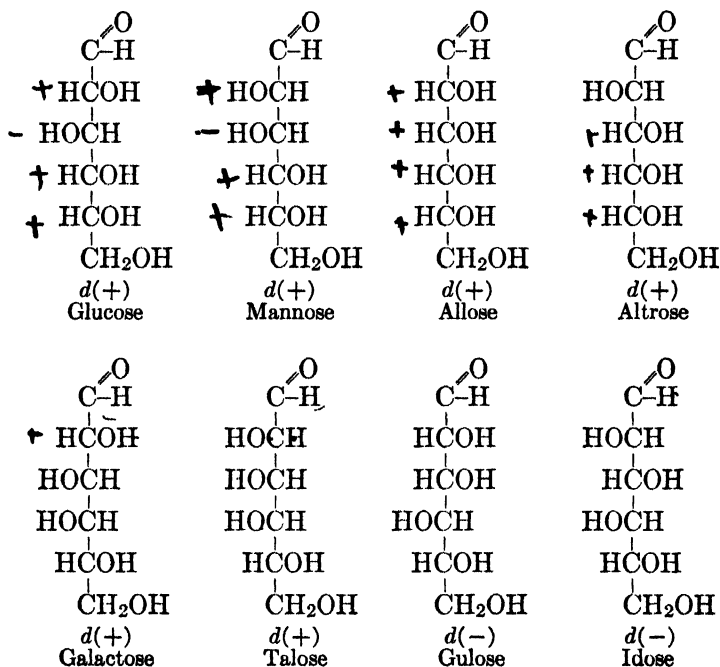
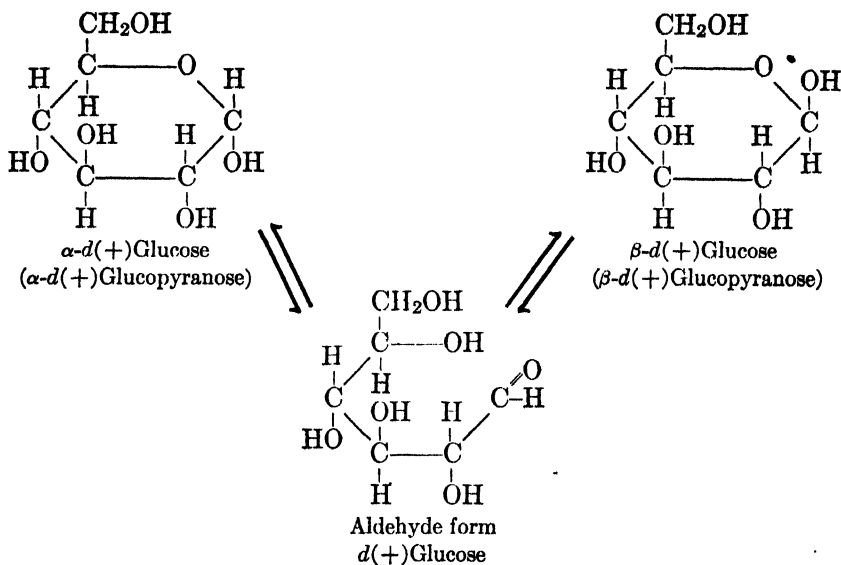
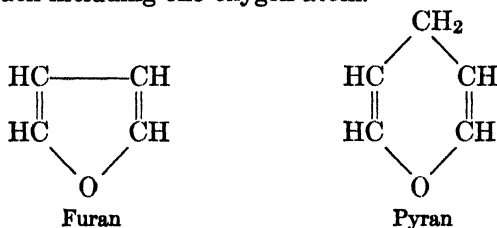


FIG. 15. The *d* aldohexoses.

chemists. However, when the spontaneous reaction of an alcohol with an aldehyde (p. 68) is recalled, the reason becomes clear. *d*(+)-Glucose contains an aldehyde group and several hydroxyl groups, so it might be expected to form a cyclic hemiacetal (sometimes called a lactol) containing either a five- or six-membered ring. It has been shown that in most cyclic *d*(+)-glucose derivatives the ring has six members. When ring formation occurs, the carbonyl carbon atom changes to the *asymmetric* hemiacetal carbon atom. This new asymmetric carbon atom may take either the *d* or *l* configuration, so there *must be two diastereoisomeric hemiacetal (lactol) forms of d(+)-glucose*. The three forms of *d*(+)-glucose can then be represented as follows.



In some cyclic derivatives of sugars five-membered rings are present. It is therefore desirable to have a method of indicating, in the name, whether a cyclic sugar contains a five- or six-membered ring. This is done by naming those with five-membered rings as furanoses and those with six-membered rings as pyranoses. Examples of this system of naming are used above in parentheses. The names are derived from furan and pyran, cyclic compounds of five- and six-membered rings, respectively, each including one oxygen atom.



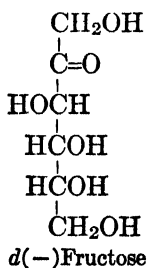
Since hemiacetal formation is reversible it is to be predicted that a solution of *d*(+)-glucose contains all three forms. Reagents which convert glucose to two isomeric products are those which attack the hemiacetal forms, whereas a substance which reacts with the open chain form yields a single product.

The equilibrium between the three forms also accounts for the *mutarotation* of *d*(+)-glucose. Two pure crystalline forms of *d*(+)-glucose have been isolated. One of them has a specific rotation of  $+113.4^\circ$  in a freshly prepared solution, but as the solution stands, the rotation

drops until it becomes constant at  $+52.2^\circ$ . The other form shows an initial specific rotation of  $+19^\circ$ , but this value slowly increases and becomes constant at  $+52.2^\circ$ . The isomer of initial rotation  $+113.4^\circ$  is  $\alpha$ - $d$ (+)-glucose; in solution it changes to the open chain form and this changes to both the  $\alpha$  and  $\beta$  forms. When equilibrium between the three forms is established the rotation is  $+52.2^\circ$ . The same equilibrium is established when pure  $\beta$ - $d$ (+)-glucose (rotation  $+19^\circ$ ) is dissolved.

It is a singular fact that the pure aldehyde form of  $d$ (+)-glucose has not been isolated. It is believed that only traces of it exist in solution in equilibrium with the cyclic forms and that the glucose of commerce (corn sugar) is a mixture of approximately the same composition as the equilibrium mixture. This view is not in contradiction with the fact that  $d$ (+)-glucose behaves as an aldehyde toward certain reagents. As the reagent combines with the trace of aldehyde form present, more of the latter is produced from the cyclic forms until eventually all of the  $d$ (+)-glucose has been consumed.

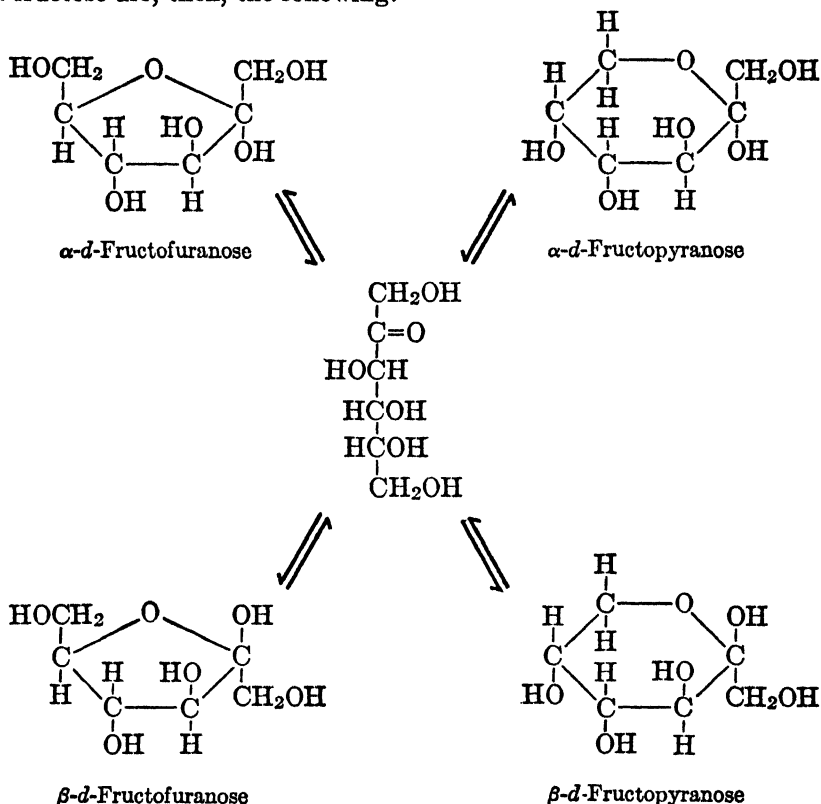
**Fructose.** Fructose, also called levulose or fruit sugar, is widely distributed in nature. It is levo-rotatory, hence the name levulose; the specific rotation is  $-93^\circ$ . Fructose has the same molecular formula ( $C_6H_{12}O_6$ ) as the aldohexoses. By methods similar to those used in the study of the structure of  $d$ (+)-glucose it has been found that fructose is a pentahydroxy ketone (a ketohexose). The ketone group has been located at the position second from the end of the chain, and it has been found that each asymmetric carbon atom in fructose has the same configuration as the corresponding one in  $d$ (+)-glucose. The projection formula of fructose can then be written as follows:



From the relationship to  $d$ (+)-glucose it is evident that ordinary fructose is a member of the  $d$  series and is correctly designated as  $d$ (-)-fructose.

Although the simple ketones do not react with alcohols (p. 78), this reaction does occur with hydroxy ketones when the two functional groups are so situated that a five- or six-membered ring may be formed. It would be predicted, therefore, that  $d$ (-)-fructose should exhibit the

phenomenon of mutarotation, and this is found to be true. The  $\alpha$  and  $\beta$  forms which have been isolated are pyranoses, but in its most important derivative  $d(-)$ fructose exists in a furanose form. The five forms of  $d$  fructose are, then, the following:



**The Aldopentoses.** The aldopentoses have one less  $>\text{CHOH}$  group than have aldohexoses. The number of asymmetric carbons is three and, consequently, there should be four pairs of optical antipodes. These are all known and are shown in Fig. 16. The formulas of only the  $d$  forms are given.

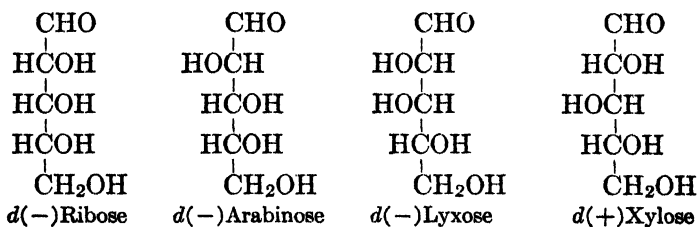


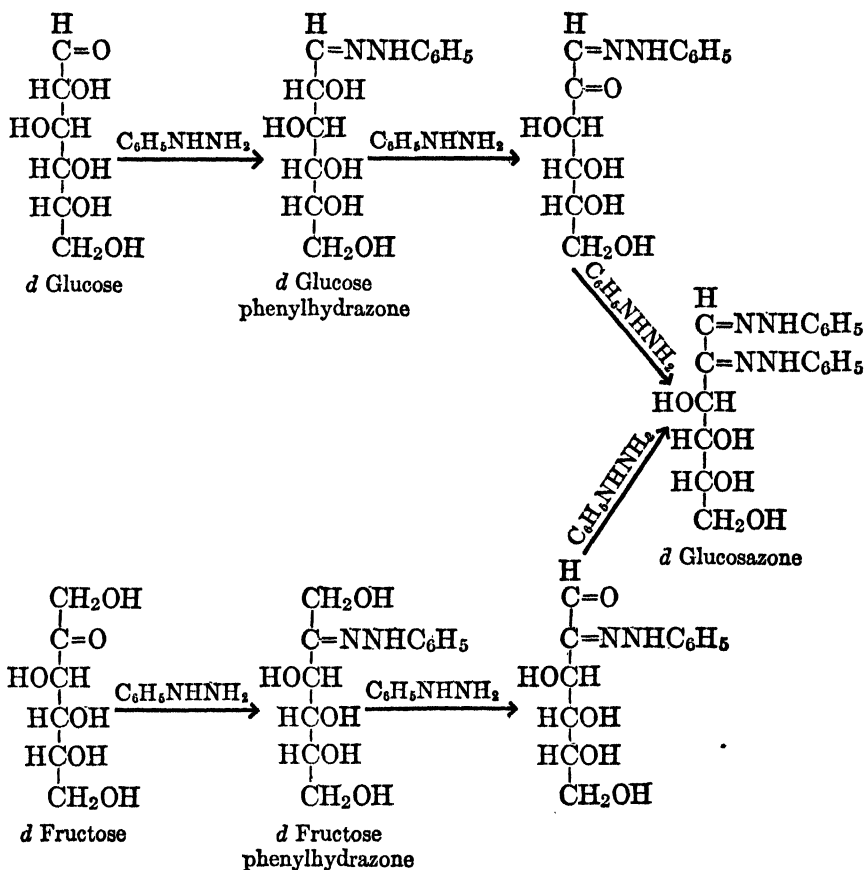
FIG. 16. The aldopentoses.

### Reactions of the Monosaccharides

**The Benedict Test.** All the monosaccharides are mild reducing agents and all give positive tests with Benedict's or Fehling's solution (p. 68). It is not surprising that the aldoses respond to mild oxidizing agents, since the test is characteristic of aldehydes. The oxidation of a ketose by these reagents must, however, involve a reaction of a somewhat different type. Actually, it has been found that  $\alpha$ -hydroxy ketones in which the alcohol group is primary or secondary are oxidized to keto aldehydes or diketones under very mild conditions  $(-\text{CH}-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}- + [\text{O}] \longrightarrow -\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-)$ . All ketoses are capable of this type of oxidation.

Sugars which reduce Fehling's or Benedict's solutions are known as *reducing sugars*. This class includes all the monosaccharides and most of the common disaccharides (p. 195). Reducing sugars are sometimes determined quantitatively by these reagents. In the quantitative procedure the cuprous oxide is separated, dried, and weighed.

**Formation of Osazones.** All reducing sugars react with phenylhydrazine to give products known as *osazones*. The reaction proceeds in three steps. In the first, the aldehyde or ketone group of the sugar reacts in the normal fashion to give a phenylhydrazone. The phenylhydrazone then reduces a second molecule of phenylhydrazine (to aniline and ammonia) with the formation of a new carbonyl group in the phenylhydrazone molecule. In the last step the newly formed carbonyl group reacts to give a second phenylhydrazone linkage. The product is the osazone, which is usually insoluble in water and crystallizes from the hot reaction mixture. Osazone formation is illustrated by the accompanying equations for the reactions of *d*(+)-glucose and *d*(-)-fructose with phenylhydrazine. The osazones are of great value in the laboratory study of carbohydrates for several reasons. Because of their low solubility they are usually easily isolated and purified, whereas many of the sugars are extremely soluble in water and crystallize with great difficulty. Different sugars are converted to osazones at different rates, and different osazones crystallize in definite, characteristic patterns. Consequently, it is often possible to identify a sugar by converting it to the osazone, noting the time required for the reaction, and observing the melting point and crystal form of the product. Hydrolysis of osazones yields dicarbonyl compounds known as *osones*.



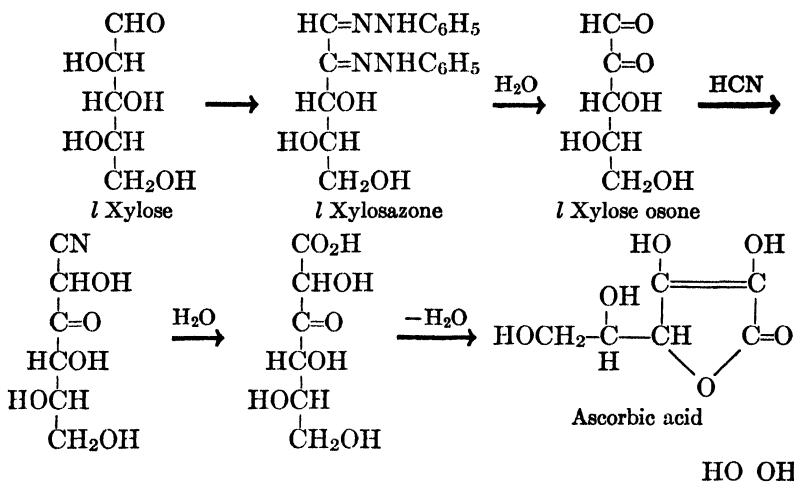
The fact that dextro-rotatory glucose and levo-rotatory fructose are converted to the *same* osazone (see equations) is of unusual interest. Once the configuration of the asymmetric carbon atoms in *d* glucose had been established, this single observation was sufficient to show that the three asymmetric atoms in *d* fructose have the same configurations as the corresponding three in *d* glucose. If this were not true, then two diastereoisomeric osazones would be produced. From the same reasoning, it can be seen that once it is known that *d* glucose is a member of the *d* series, then ordinary fructose must be *d* fructose.

A similar relationship obtains between ribose and arabinose; their osazones are identical. Lyxose and xylose also yield osazones that are the same.

**Ascorbic Acid.** One of the most important derivatives of xylose is ascorbic acid or vitamin C. A deficiency of this substance in the diet causes scurvy. The vitamin occurs in fruits and vegetables, notably in



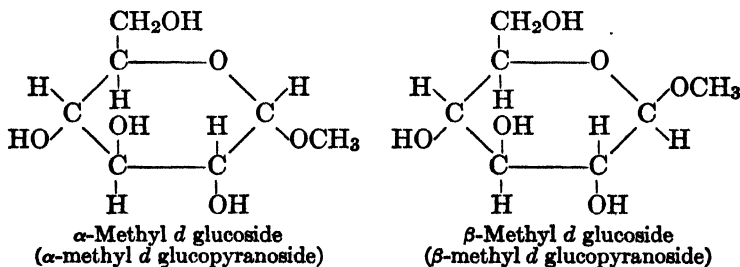
citrus fruits, tomatoes, and fresh peppers. It has been synthesized from *l* xylose by the following sequence of transformations.



Ascorbic acid is the enol form of a keto lactone. The group  $\text{---C}=\text{C---}$  is known as the enediol group. The acidity of the compound is due to the hydroxyl group in the *beta* position.

**Glycosides.** Reduction and osazone formation are reactions of the *carbonyl* forms of the monosaccharides. The most important derivatives of the cyclic hemiacetal or lactol forms are the acetals. In this connection it should be recalled that simple hemiacetals react with alcohols to give acetals (p. 70). The hemiacetal forms of the sugars react in the same way, yielding acetals which are known by the class name of *glycoside*. Particular compounds of this type are named after the sugars from which they are derived. Thus glycosides obtained from glucose are glucosides, and those from fructose are fructosides. If it is desired to make the names still more specific, to show the size of the rings, this is done by incorporating the stems furan and pyran (p. 189) in the names.

Examples of glycosides are the two methyl glucosides obtained from *d* glucose and methyl alcohol in the presence of an acid catalyst. Their formulas are given below.

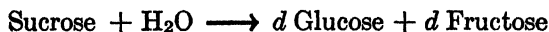
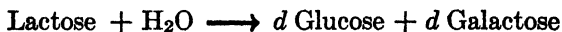


The chemical properties of the glycosides are widely different from those of the simple sugars. Because hemiacetal formation is readily reversible the monosaccharides have the properties of aldehydes or ketones, and, as already seen, mutarotation, reducing properties, and osazone formation all depend on the spontaneous change of hemiacetal forms of sugars to the carbonyl forms. Acetal formation, however, is *not* spontaneously reversible. Only on heating with water and acid do the acetals regenerate the parent aldehyde and alcohol. In consequence, the glycosides are quite stable substances. They do not exhibit mutarotation, nor do they react with phenylhydrazine or mild oxidizing agents. This is an important consideration, because the more complex sugars, the disaccharides and polysaccharides, are glycosides derived from two or more molecules of monosaccharide.

**Classification and Definitions.** From what has been said of glucose and fructose, it is seen that the monosaccharides are polyhydroxy aldehydes or ketones. Other carbohydrates can be hydrolyzed to monosaccharides in the presence of acids. It is possible to define carbohydrates as those substances which are polyhydroxy aldehydes or ketones or which upon hydrolysis yield only polyhydroxy aldehydes or ketones. According to this definition a glycoside involving one molecule of monosaccharide and one molecule of a non-sugar, such as  $\alpha$ -methyl *d* glucoside, is to be regarded as a carbohydrate *derivative*.

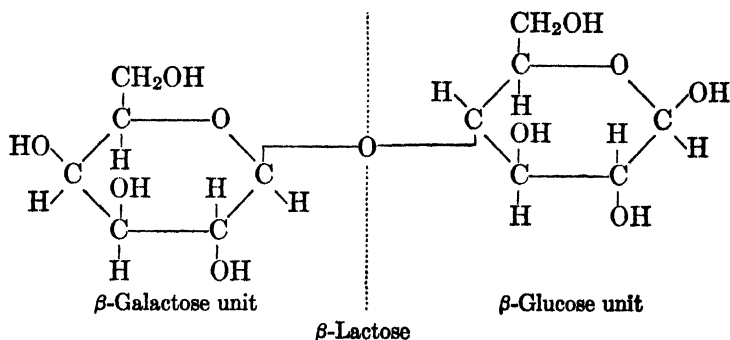
### The Disaccharides

The disaccharides have compositions which indicate that they are formed from two molecules of monosaccharide by elimination of one molecule of water. Under the influence of acids or digestive enzymes they take up one molecule of water and yield two molecules of monosaccharide. The common disaccharides are derived from the hexoses and so have the formula  $C_{12}H_{22}O_{11}$ . The two molecules of monosaccharide formed by hydrolysis may be alike or different. Thus maltose yields a single monosaccharide, while lactose and sucrose yield mixtures,

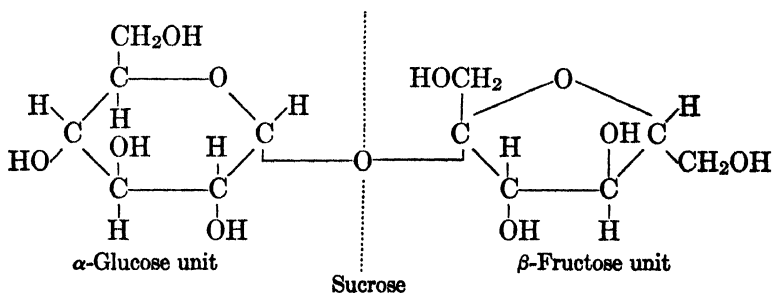


**The Structure of Maltose.** Maltose, which yields two molecules of *d* glucose upon acid hydrolysis, is a reducing sugar. It exhibits the phenomenon of mutarotation and it can be converted to an osazone. Analysis of the osazone shows that only one of the two glucose units present is involved in osazone formation. These facts indicate that the two mono-





**Sucrose.** Maltose and lactose, having reducing properties, are known as reducing disaccharides. The only important member of the other possible class, the non-reducing disaccharides, is *sucrose*, or the ordinary sugar obtained from the sugar cane and the sugar beet. Sucrose yields one molecule each of *d* glucose and *d* fructose upon hydrolysis in the presence of acids. Since sucrose is not oxidized by Benedict's reagent, does not mutarotate, and does not form an osazone, the two monosaccharide units must be combined in such a way that neither residue retains a hemiacetal linkage. *It must be at once a glucoside and a fructoside.* It has been found that the glucose residue is present as an  $\alpha$ -glucoside and that the fructose is combined as a  $\beta$ -fructofuranoside (p. 189). Its formula is the following:

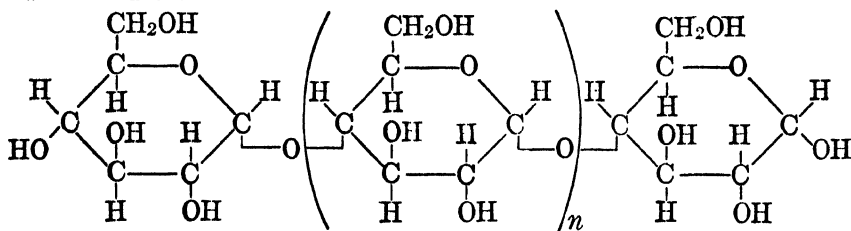


Sucrose is dextro-rotatory ( $[\alpha]_D^{20} = 66.4^\circ$ ). On hydrolysis it yields equal amounts of dextro-rotatory glucose ( $[\alpha]_D^{20} = +52.2^\circ$ ) and levo-rotatory fructose ( $[\alpha]_D^{20} = -93^\circ$ ). When hydrolysis is complete the solution is levo-rotatory, the rotation being the algebraic sum of the rotations of the two monosaccharides ( $[\alpha]_D^{20} = -40.8^\circ$ ). Because of the change in sign the process is called *inversion*, and a mixture of equal parts of glucose and fructose prepared in this way is known as *invert sugar*. Honey is largely invert sugar.

## Polysaccharides

**Starch.** The cereal grains are composed essentially of starch. Certain roots also contain high percentages of starch; the potato contains about 18 per cent of this component. The granules of starch produced by different plants vary in size and shape, so it is possible to determine the source of a sample of starch by examination under a microscope. In their chemical properties the starches from different sources are identical.

The analysis of starch shows that it has the composition  $(C_6H_{10}O_5)_n$ . Hydrolysis by enzymes or acids converts starch into *d* glucose, so it is evident that the unit  $C_6H_{10}O_5$  is a *d* glucose residue. Maltose is among the products of incomplete hydrolysis, indicating that the glucose units are linked together in the  $\alpha$ -glucoside form. From these and other observations of the chemical behavior of starch the following structure has been deduced.



Until recently it was believed that the starch molecule consisted of 24 to 30  $\alpha$ -glucose units joined together as shown in the above formula ( $n = 22$  to 28). However, it is now becoming evident that the molecule is much larger. It appears that the chains of about 25 glucose residues are united by a linkage different from that which joins the glucose units in the chains. The number of chains composing the starch molecule is unknown, but it is likely that the molecule contains several hundred glucose units rather than about twenty-five.

Because of its high molecular weight starch does not give a true solution in water. However, it does give colloidal dispersions, ranging from jellies to mobile liquids as the concentration of starch is diminished. These "solutions" of starch do not respond to the Benedict or Fehling test. This indicates that the chains of glucose units are combined in the starch molecule in such a way that the hemiacetal group at the end of each chain is involved.

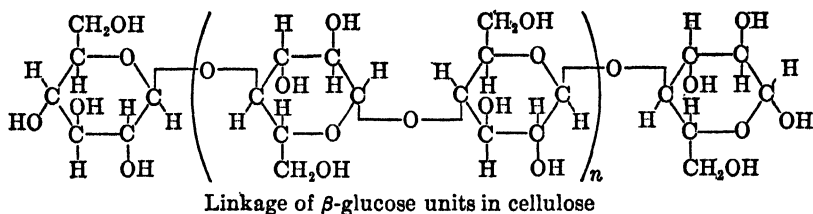
Partial hydrolysis of starch converts it into smaller molecules known as dextrins. Dextrins are also obtained by heating starch to 200–250°; the gloss of starched cloth is due to the formation of dextrins when the cloth is ironed. Dextrins are used in the preparation of mucilages.

Continued hydrolysis converts starch into maltose and finally into glucose. Under the influence of the enzyme diastase, obtained from sprouted barley, the hydrolysis product is maltose. The commercial hydrolysis of starch is usually carried out in the presence of very dilute hydrochloric acid. After hydrolysis has proceeded to the desired stage the acid is neutralized and the solution is evaporated to give a thick syrup which contains dextrins, maltose, and glucose. This syrup, usually known as "corn syrup" since the starch is obtained from corn, is widely used as a sweetening agent. Pure *d* glucose is also prepared commercially by the complete hydrolysis of starch.

A deep blue color is produced when iodine is added to a solution of starch. This is the basis of a very sensitive test for either starch or iodine. With dextrins the result may be a color ranging from violet to red or no color at all, depending upon the degree of degradation. Maltose and glucose do not give colors.

The normal human diet contains more of carbohydrate than of fat and protein combined, and the greater part of the carbohydrate is starch. Digestion of starch consists in its hydrolysis to glucose. The saliva contains the enzymes ptyalin, which catalyzes the hydrolysis of starch to maltose, and maltase, which converts maltose to glucose. The gastric juice contains no starch-splitting enzyme, but digestion of carbohydrate in the stomach continues under the influence of the salivary enzymes. Several amylases (the general name for starch-splitting enzymes) and maltases are present in the pancreatic and intestinal juices, as are also certain enzymes which bring about the hydrolysis of disaccharides such as sucrose and lactose. Thus practically all the starch and sugar ingested is converted to monosaccharides. These are absorbed through the intestinal wall and are carried to the liver by the blood stream. In the liver glucose is recombined to form *glycogen*, a polysaccharide very similar to ordinary starch but apparently of lower molecular weight. Hydrolysis of glycogen converts it wholly to glucose. However, the liver produces it from all the hexoses normally liberated in the small intestine (glucose, fructose, and galactose). The glycogen stored in the liver is a reserve supply of carbohydrate for the body. When sugar is required by other parts of the body, liver glycogen is hydrolyzed to glucose, and the latter is discharged into the blood stream. The muscles remove glucose from the blood and convert it to muscle glycogen. The energy required for muscular work is obtained by a complex process involving the indirect oxidation of glycogen. Also, the energy required for maintenance of body temperature is obtained in part from the oxidation of glycogen.

**Cellulose.** Cellulose, which constitutes the greater portion of plants, is a polysaccharide which can be represented by the formula  $(C_6H_{10}O_5)_n$ . This is identical with the empirical formula of starch, and cellulose, like starch, is converted to *d* glucose by hydrolysis in the presence of acids. However, there are two important differences in the structures of the two polysaccharides. In the first place, the monosaccharide unit of cellulose is  $\beta$ -glucose, rather than  $\alpha$ -glucose as in starch. Secondly, the molecular weight of cellulose is much greater than that of starch. It appears that several thousand  $\beta$ -glucose units are involved in the giant molecule.



Hydrolysis of cellulose under severe conditions and in the presence of acids produces glucose, as mentioned above. If the hydrolysis is incomplete the reaction mixture is found to contain cellobiose, a disaccharide which differs from maltose only in that it is a  $\beta$ -glucosido-glucose. In the condensed formula for a cellulose chain given above the unit enclosed by the brackets is a cellobiose residue. The human digestive system provides no enzymes capable of splitting cellulose, but certain animals are able to utilize part of the ingested cellulose.

Natural cotton is one of the purest forms of cellulose. The fibers of raw cotton are covered with a waxy substance which acts as a sizing, making the fibers waterproof. Absorbent cotton is made by extracting the natural sizing with organic solvents. Linen, made from flax, is also essentially cellulose; it is not so pure as cotton.

Wood contains cellulose and lignin, a substance of high molecular weight, whose structure is not yet definitely known. When cellulose is heated with strong hydrochloric acid it is hydrolyzed to a mixture of sugars. This process, as a preparation of edible sugar from wood, has been reported to be in large scale operation in Germany.

The manufacture of paper is an important cellulose industry. The raw material is usually wood, and the principal operation in converting it to paper is the removal of lignin. The wood is first shredded to separate the fibers and then heated with a solution of some chemical, such as sodium sulfite, to extract the lignin. The purified cellulose is collected on screens, rolled, and dried. Various additional processes are required, depending on the type of paper desired. For instance, bleaching

is necessary to produce a white paper. Writing paper is impregnated with sizes, such as rosin, glue, starch, and silicates. Parchment paper is prepared by immersing the sheets in cold, concentrated sulfuric acid. This treatment renders the surface waterproof. The best grades of paper are made from cotton rags, that is, from quite pure cellulose. Some paper is made from straw.

### Cellulose Derivatives

**Cellulose Nitrate.** From the structural formula written above for a portion of the cellulose molecule it can be seen that three alcohol groups are present in each glucose unit. These show many of the reactions of ordinary alcohols. For example, treatment of cellulose with a mixture of sulfuric and nitric acids produces the nitrate,  $[C_6H_7O_2(ONO_2)_3]_x$ , in which each hydroxyl group has been esterified by nitric acid. This product is known as cellulose trinitrate or guncotton. It is a high explosive of great military value. If the reaction with nitric acid is carried out under milder conditions a mixture of mono- and dinitrates is formed. This material, known as pyroxylin, finds many uses. *Smokeless powder* is a mixture of pyroxylin and guncotton. *Celluloid* is a mixture of camphor and pyroxylin. *Collodion* is a solution of pyroxylin in alcohol and ether. Certain *lacquers* are essentially solutions of pyroxylin in butyl acetate or other solvents. The pyroxylin is first treated with dilute alkali, a process which makes it more soluble in organic solvents and renders the solutions less viscous. The lacquer must also contain coloring materials, resins, and certain very high-boiling liquids (plasticizers) which increase the elasticity of the dry lacquer film. It is to be noted that the drying of lacquers involves only the evaporation of a solvent, whereas the "drying" of oil paints depends on chemical reactions initiated by the oxygen of the air.

**Cellulose Acetate.** Acetic anhydride converts cellulose to the triacetate  $[C_6H_7O_2(OCOCH_3)_3]_x$ . Cellulose acetate is soluble in various solvents, and it can be obtained in the form of thin sheets by evaporation of its solutions. Cellulose acetate is much less inflammable than pyroxylin and has supplanted the latter in certain products which are subjected to fire hazards. When mixed with suitable plasticizers the acetate can be molded. Cellulose acetate has been widely used as the bonding sheet in safety glass.

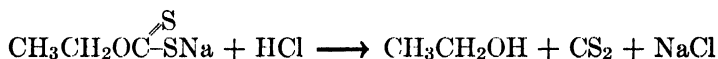
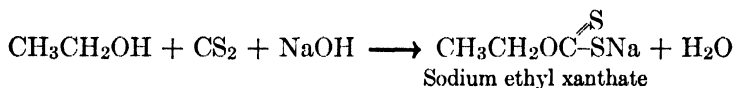
**Rayon.** It has been found that the difference in the appearance of silk and cotton materials depends on the fact that the silk fibers are long, smooth, tubular threads, whereas those of cotton are short and irregular. The first process developed for improving the appearance of



cotton fabrics was mercerization, which is a brief treatment with alkali. It imparts a sheen to the cloth, but since it affects only the surface of the fibers the appearance of the product is still quite different from that of silk. In making rayon, cellulose is converted into a soluble derivative, and a solution of the derivative is forced through fine holes into a medium which alters the derivative or removes the solvent so that a filament is formed.

The acetate process for making rayon employs a solution of cellulose acetate in a volatile organic solvent. The solution is spun into a heated chamber so that the solvent evaporates, leaving a filament of cellulose acetate (acetate rayon).

Other processes are designed to give filaments of *regenerated cellulose*. The most extensively used is the viscose process, in which cellulose is converted into the soluble cellulose xanthate. The xanthate solution is spun into a bath of acid, which decomposes the xanthate and precipitates cellulose. The formation and decomposition of a xanthate can be illustrated with a simple alcohol. The reagents are sodium hydroxide and carbon disulfide.



In the preparation of cellulose xanthate the cellulose is first treated with alkali. The "sodium cellulose" so obtained is a somewhat degraded cellulose probably containing both adsorbed and combined alkali. On treatment with carbon disulfide the xanthate is formed. Colloidal dispersions of cellulose xanthate are extremely viscous, hence the name, viscose. In the preparation of cellophane the xanthate solution is forced through narrow slits into the regenerating bath.

The cuprammonium process makes use of the soluble derivative formed when cellulose is treated with an ammoniacal solution of a copper salt (Schweitzer's reagent). The derivative is decomposed by acids to regenerate the cellulose.

In the practical application of these processes a number of modifications are necessary. Various substances are added to the solutions of the cellulose derivatives to improve the spinning properties and increase the flexibility of the filaments. Glycerol and glucose are among the substances added. A number of washings of the filaments are required to remove the various chemicals used in each process, and bleaching is necessary. In the preparation of cellophane numerous washing and

rolling operations are required, and the product is finally coated with a lacquer to make it waterproof.

An idea of the industrial importance of rayons may be gained from the consideration that the annual production in the United States is approaching 200,000 tons. In the early development of the industry, low-grade cotton was used as the raw material. With the improvement in methods of processing wood, more and more of the cellulose is being obtained from this source.

### PROBLEMS

1. Define and illustrate the following terms: (a) aldopentose, (b) ketohexose, (c) reducing sugar, (d) lactol, (e) mutarotation, (f) invert sugar, (g) glycoside, (h) glucoside, (i) osazone, (j) pyranose, (k) furanose, (l) polysaccharide, (m) dextrin, (n) glycogen.

2. A new sugar is found to exhibit mutarotation; predict its behavior toward: (a) Benedict's solution, (b) methyl alcohol and hydrochloric acid, (c) phenylhydrazine.

3. By means of equations, show the reactions involved in the preparation of rayon, gunpowder, lacquers, cellophane, and edible sugars from cellulose.

4. Compare the structures of  $\alpha$ -methyl *d* glucoside, maltose, dextrin, and starch. Compare the structure of starch with that of cellulose.

## CHAPTER XVI

### VALENCE

Since the time of Kekulé many theories have been developed regarding the nature of valence. The most successful of these is the electronic theory of valence originated by Kossel and Lewis. It grew out of the experiments and speculations of Werner and others and was later amplified by Langmuir and interpreted by Sidgwick.

The chief practical value of the electronic theory is that it provides an explanation of the different kinds of valence; for valence had come to mean to the organic chemist something very different from the classical concept of the inorganic chemist. Inorganic compounds are generally salts, acids, or bases—compounds possessing polar properties. Organic compounds, on the other hand, are generally nonpolar in character. The contrast between these two classes of substances is seen best by reference to their physical properties. Some of these are listed below.

NONPOLAR COMPOUNDS	POLAR COMPOUNDS
Volatile	Nonvolatile
Low melting points	High melting points
Insoluble in water	Soluble in water
Soluble in organic solvents	Insoluble in organic solvents
Un-ionized in solution	More or less completely ionized in solution
Fixed bonds which permit structural isomerism	No isomerism
Reactions slow	Reactions rapid

These properties represent the extreme cases of polar and nonpolar substances. Most compounds fall somewhere between the two extremities of the series, and all gradations are observed.

An example of an extremely polar compound is sodium chloride. Most inorganic salts belong in this category. Saturated hydrocarbons such as methane exemplify the extremely nonpolar group.

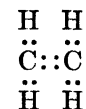
### TYPES OF VALENCE

Any theory of valence must be able to account for the great difference in these two groups. The electronic theory does this by providing a means of representing *different kinds* of valence. This theory assumes that a bond is formed by a pair of electrons shared between two atoms.

Each atom except those of the inert gases has one or more electrons available for bond formation. These are known as valence electrons, and the number is related to the position of the element in the periodic table. Thus sodium has one, magnesium two, aluminum three, carbon four, nitrogen five, oxygen six, and chlorine seven.

It is postulated that in a nonpolar compound a valence bond is formed by two electrons—one from each of the atoms involved. Such a bond is called covalent or nonpolar and is highly localized; it has a fixed direction. Thus the hydrogen molecule is represented as  $\text{H}:\text{H}$ . Similarly,

methane is  $\begin{array}{c} \text{H} \\ \vdots \\ \text{H}:\text{C}:\text{H} \\ \vdots \\ \text{H} \end{array}$ . Ethylene and acetylene are written in the following manner:



Ethylene

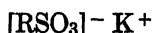
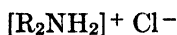
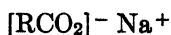


Acetylene

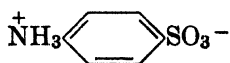
It is evident that these representations differ from the line formulas commonly used by organic chemists only in that a pair of dots has replaced a line. Clearly in such cases the electronic formulas offer as yet little or no practical advantage over the line formulas.

The case of sodium chloride is very different. Here an electron has passed from the sodium atom to the chlorine atom and the formula is  $\text{Na}^+\text{Cl}^-$ . In other words, the two ions are held together only by electrostatic forces. This relationship, characteristic of polar compounds, is generally spoken of as electrovalence. The binding force is not localized but is exerted in all directions and affects all ions of the opposite charge which happen to be near.

This type of linkage is not ordinarily formed by carbon but is found in salts of organic acids and amines.



Amino acids have saltlike or polar characteristics and may be represented as inner salts.



These are known as zwitterions (p. 174).

Compounds whose properties are intermediate between those of the extreme polar and nonpolar categories are supposed to have one or more

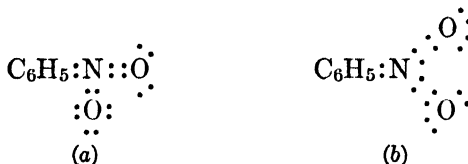
bonds in which the electron pair is *shared unequally* by the two atoms.

Thus methyl alcohol may be pictured as follows: 
$$\begin{array}{c} \text{H} \\ \vdots \\ \text{H}:\text{C}:\ddot{\text{O}}:\text{H} \\ \vdots \\ \text{H} \end{array}$$
 The

electron pair joining the hydrogen atom to the oxygen atom is represented as being predominantly in the possession of the oxygen atom. This distribution of the electrons creates a dipole approaching the truly polar type in which the electrical charges are entirely separate. This explains why methyl alcohol is more polar than methane and why sugars—with many such hydroxyl groups—show a marked polar character in many of their physical properties.

### The Coordinate Covalence

A special type of covalent linkage known as the coordinate covalence (also called semipolar) bond occurs frequently. It is present, for example, in the nitro group. The accepted formula for nitrobenzene is represented by *a*.



Here it will be observed that both oxygen atoms as well as the nitrogen atom have shells of eight electrons. Structure *b*, which corresponds to

the line formula  $\text{C}_6\text{H}_5-\text{N} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{O} \end{array}$ , is seen to be unlikely because it violates the

octet rule, the nitrogen atom having a shell of ten electrons. Most negative atoms tend to acquire electrons and reach a saturation point at eight. It follows that the maximum valence of these elements is four. In *a* the nitrogen atom holds four electron pairs and thus is tetravalent.

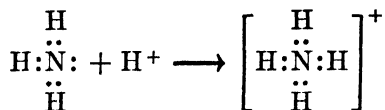
It will be noticed, however, that the single bond between nitrogen and oxygen is peculiar in that both of the electrons of the bonding pair come from one atom. This is true of all coordinate covalent bonds. The atom furnishing the electron pair is called the *donor*; the other atom is known as the *acceptor*. In sharing the pair the nitrogen atom virtually gives up one electron to the oxygen atom. The nitrogen atom will, accordingly, carry a positive charge. The oxygen atom, on the other hand, will possess a negative charge. This is a typical coordinate covalent linkage.

The formula might be written  $\text{C}_6\text{H}_5-\text{N}^+-\text{O}^-$  or  $\text{C}_6\text{H}_5:\text{N}^+:\ddot{\text{O}}:^-$  to show

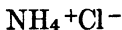
this. The notation generally used is  $\text{C}_6\text{H}_5-\text{N}=\text{O}$ . That is, the coordinate

covalent bond is represented by an arrow pointing from the *donor* to the *acceptor*.

Ammonium chloride offers a striking illustration of types of valence. Consider the reaction between ammonia and hydrogen ion.

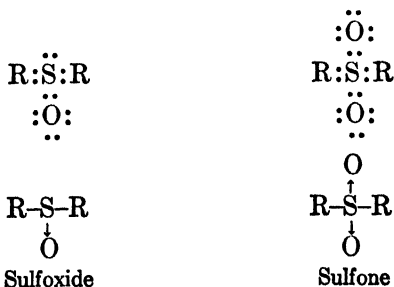


The nitrogen atom in ammonia is trivalent but has in addition an unshared pair of electrons which permits it to form a linkage with the proton, giving rise to the ammonium ion. Thus, in ammonium chloride the chloride ion is held by an electrovalence.



Amine oxides (p. 397), formerly written  $\text{R}-\text{N}=\text{O}$ , are now represented as  $\text{R}:\ddot{\text{N}}:\ddot{\text{O}}:$  or  $\begin{array}{c} \text{R} \\ \vdots \\ \text{R}-\text{N}-\text{O} \\ \vdots \\ \text{R} \end{array}$ , the oxygen atom being joined to the nitrogen atom by a coordinate covalent bond.

Sulfoxides and sulfones (p. 63) are to be written similarly.



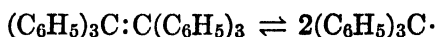
In sulfoxides the sulfur atom is really trivalent and not tetravalent as represented in the line formulas. Similarly, in sulfones the sulfur atom is tetravalent and not hexavalent.

The new point of view accords well with the chemical behavior of these substances. If they really had double linkages between sulfur and oxy-

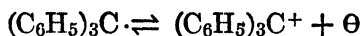


### Free Radicals

Another very great advantage gained by the use of two dots for a valence bond is that the bond can be separated into two parts. Thus the dissociation of hexaphenylethane into the free radical, triphenylmethyl, can be pictured as follows:



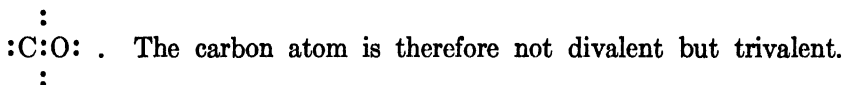
In general free radicals may be represented as having a trivalent carbon atom with one additional (unshared) electron. In liquid sulfur dioxide the dissociation is ionic and can be indicated as follows:



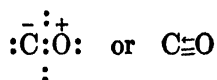
This means that in sulfur dioxide solution the free radical is in equilibrium with the triphenylmethyl cation and an electron. Both the ion and the electron are believed to be solvated by the sulfur dioxide. Here are seen examples of trivalent carbon with no extra electrons (positive ion) and with one extra electron (free radical). The electronic theory enables one to represent these satisfactorily whereas the line formulas furnished no adequate means of notation for such instances.

### "Divalent" Carbon Atoms

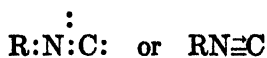
Carbon monoxide and certain other molecules long supposed to contain divalent carbon atoms can also be clearly represented by use of electron bonds. Carbon monoxide is now believed to have the structure



Nevertheless, the valence state is again different from any of the three examples of trivalent carbon just considered in connection with free radicals. In carbon monoxide the carbon atom and the oxygen atom have five electrons each (one pair and half of three pairs) and therefore are joined not only by two nonpolar or covalent bonds but also by a coordinate covalent linkage as well. The formula may be written

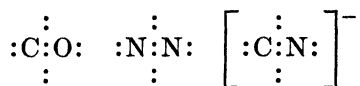


The isonitriles can be represented similarly.

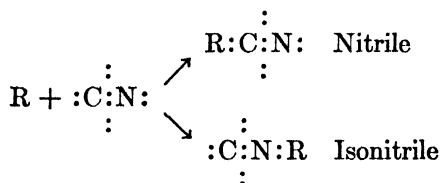




It is interesting to compare the cyanide ion with nitrogen and carbon monoxide. All have the same valence arrangement.



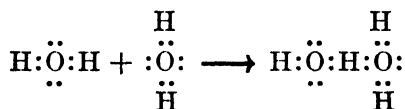
The union of the cyanide ion with a positively charged alkyl radical is a coordination and may take place in either of two ways, producing in the one instance a nitrile and in the other an isonitrile.



### The Hydrogen Bond

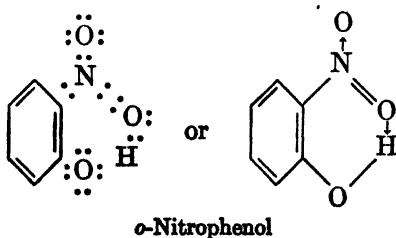
Recently it has been shown that a hydrogen atom can form a bridge between two other atoms if they are very electronegative in character. Oxygen, fluorine, and nitrogen may be joined in this way. As would be expected, the link between two fluorine atoms is the most stable. It exists in potassium hydrogen fluoride ( $\text{KHF}_2$ ), the formula of which is written  $\text{K}^+[\text{:}\ddot{\text{F}}\text{:}\text{H}:\ddot{\text{F}}\text{:}]^-$ .

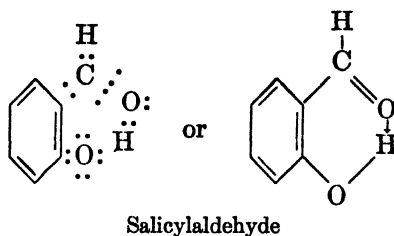
The association of water and other hydroxyl-containing compounds has been ascribed to the formation of a hydrogen bridge between two oxygen atoms.



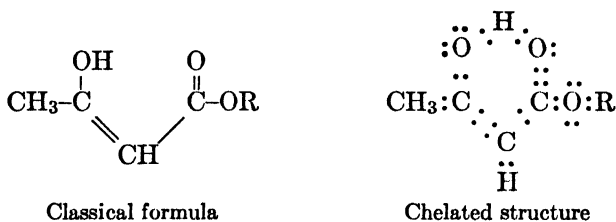
### Chelate Rings

This type of linkage is believed to exist in many ortho disubstituted benzene derivatives. For example, *o*-nitrophenol and salicylaldehyde may be written as follows:

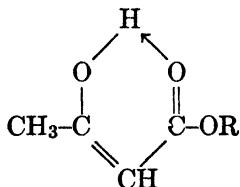




Nearly all enols can be formulated as ring compounds in which the ring is closed through a hydrogen bond. It is believed that enolization always involves hydrogen bond formation. Acetoacetic ester will serve as an example.

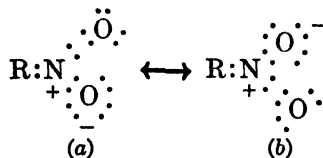


Such rings are known as chelate rings and are often represented in the following way:



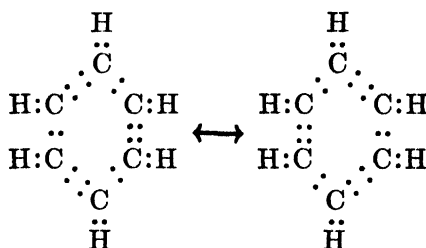
### The Resonance Principle

Many organic molecules are capable of existing in two or more equivalent or nearly equivalent electronic arrangements. The nitro compounds are examples.

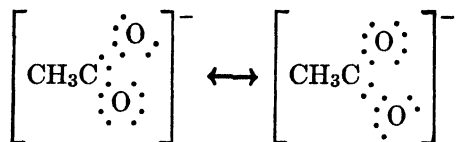


Forms *a* and *b* are equivalent; the molecule is correctly represented by neither form alone but by both simultaneously. The phenomenon is known as resonance. Resonating molecules cannot, therefore, be represented adequately by our formulas.

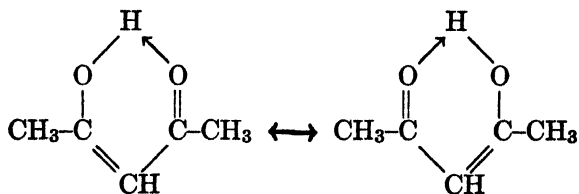
Resonating molecules are always more stable than would be expected from an examination of their structural formulas as ordinarily written. Benzene is a striking illustration.



A simpler example is seen in the acetate ion.



Conjugated pairs of double bonds are resonating systems and lend an abnormally large stability to molecules in which they occur. Enols illustrate this type. In general the enol form resonates whereas the corresponding keto form does not. This accounts to some extent for the tendency of the enols to chelate by hydrogen bond formation. The enol modification of acetylacetone, for example, has the following resonance forms:



### PROBLEM

Write electronic formulas for the following substances:



## SUGGESTED READINGS

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## CHAPTER XVII

### ISOMERISM

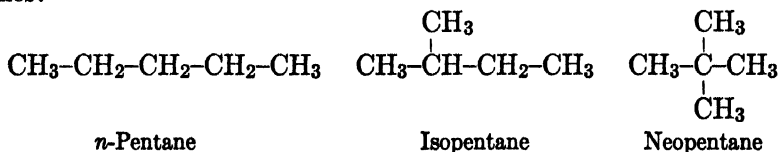
Isomerism is characteristic of complex molecules held together by fixed or covalent bonds and is, therefore, confined primarily to carbon compounds. Isomers have the same molecular formula but differ in at least one of their chemical or physical properties. The difference is, of course, due to a difference in the arrangement of the atoms in the molecule. Following are the principal types of isomerism.

#### TYPES OF ISOMERISM

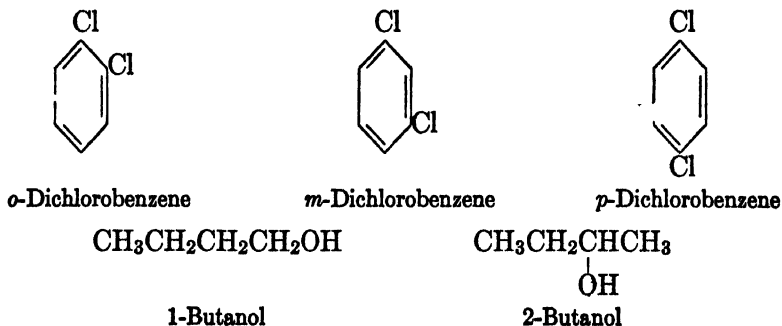
##### Simple Structural Isomerism

The difference between isomers of this group can be expressed by simple structural formulas. Ordinary planar or two-dimensional formulas are sufficient.

**Nucleus or Chain Isomers.** Nucleus or chain isomers differ in the arrangement of the carbon atoms. Examples of this are the three pentanes:



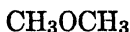
**Position Isomers.** Position isomers have the same carbon skeleton but differ in the position of some atom or group attached to it. Examples are *o*-, *m*-, and *p*-dichlorobenzene and 1- and 2-butanol.



**Functional Group Isomers.** Functional group isomers have different functional groups. Ethyl alcohol and methyl ether are examples.



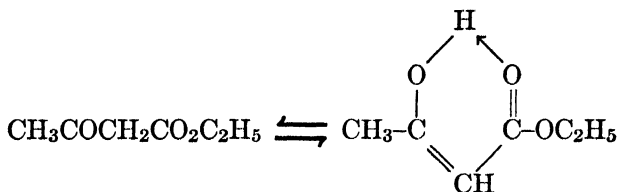
Ethyl alcohol



Methyl ether

Chain, position, and functional group isomerism often occur together.

*Tautomerism* is really a type of functional group isomerism but is often classified separately because of its unusual nature and its profound theoretical importance. In this type of isomerism two forms occur and are characterized by the fact that they are directly and readily interconvertible. The classical example is acetoacetic ester. The *enol* and *keto* modifications form an equilibrium mixture (p. 150).

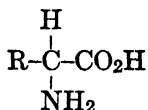


### Stereoisomerism

Stereoisomerism depends on differences in the three-dimensional space relations in molecules. There are two principal types: optical isomerism and *cis-trans* or geometrical isomerism.

**Optical Isomers.** Optical isomerism occurs in molecules which are asymmetric. In other words, any molecule which is not superimposable upon its mirror image may exist in two forms. These isomers have identical properties except for the effect on plane polarized light. The common elements of symmetry which must be absent from such a molecule are (a) a plane of symmetry and (b) a center of symmetry.

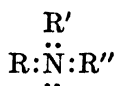
Most of the known optically active compounds owe their molecular asymmetry to the presence of an asymmetric carbon atom. The carbon atom is said to be asymmetric when it holds four different atoms or groups of atoms.  $\alpha$ -Amino acids illustrate this type.



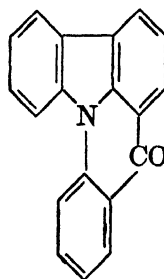
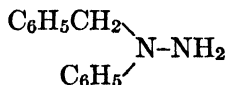
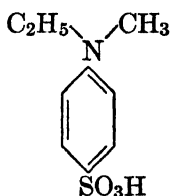
Optical activity may be due also to asymmetric atoms other than carbon. The resolvable sulfinic esters are examples. Incidentally, the dis-



atom is tetravalent have been resolved. From the knowledge that sulfinic esters are capable of existence in optically active forms, it would be expected that tertiary amines of the type



could be resolved. However, all attempts to prepare optically active forms of such amines have failed. The following are a few of the many tertiary amines whose resolution has been unsuccessfully attempted.

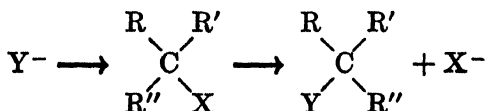


Selenium, tellurium, tin, germanium, phosphorus, arsenic, boron, beryllium, copper, zinc, and a number of other elements may give rise to optical activity when properly substituted.

### The Walden Inversion

Replacement of an atom or group attached directly to an asymmetric atom often causes a rearrangement of the groups around the latter giving a derivative which has a configuration opposite that of the original molecule. This phenomenon was discovered by Walden and is known as the Walden inversion.

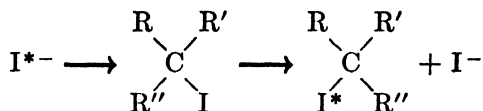
This inversion has attracted much attention, primarily because of its bearing on the problem of the mechanism of substitution in general. A suggestion that has proved very helpful is that the entering atom approaches the face of the tetrahedron opposite to the atom which is displaced.



This would bring about inversion.



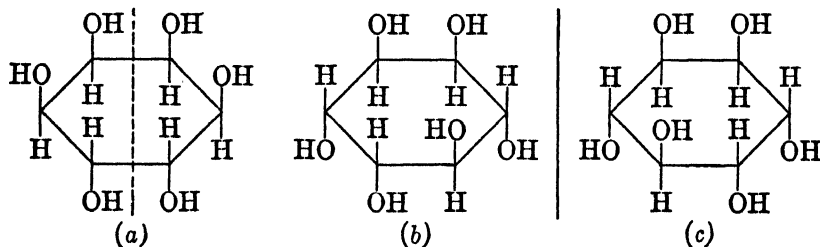
Support for this proposal has been found in the replacement of iodine by radioactive iodine in an optically active iodide.



The rate of inversion, as measured by the rate of racemization, of the original iodide is the same as the rate at which the iodide becomes radioactive.

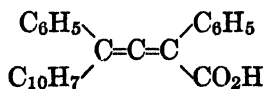
**Optically Active Compounds Which Do Not Contain an Asymmetric Atom.** For a long time it was believed that the presence of an asymmetric atom was necessary if a molecule was to be optically active. This view has changed, however, with the discovery of numerous optically active substances whose structures contain no asymmetric atom. These fall into several distinct groups each of which will now be examined briefly.

**The Inositol Type.** Inositol is a hexahydroxycyclohexane and exists in eight different forms, two of which are represented here.



Seven of these isomers have one or more planes of symmetry and are optically inactive; an example is represented by figure *a* whose plane of symmetry is indicated by the dotted line. The eighth form of inositol, however, has no plane of symmetry or center of symmetry. Furthermore, it has no asymmetric carbon atom. Yet it exists in *d* and *l* forms as shown in figures *b* and *c*.

**The Allene Type.** Early in the development of stereochemistry it was recognized that properly substituted allenes should be asymmetric molecules and, therefore, should be resolvable into *d* and *l* forms. Although many chemists have sought to obtain such optically active allenes it was only recently that success was achieved. The first allene to be resolved was the following:



**The Spirans.** These are very similar to the allenes. Following are three which have been resolved into *d* and *l* forms:

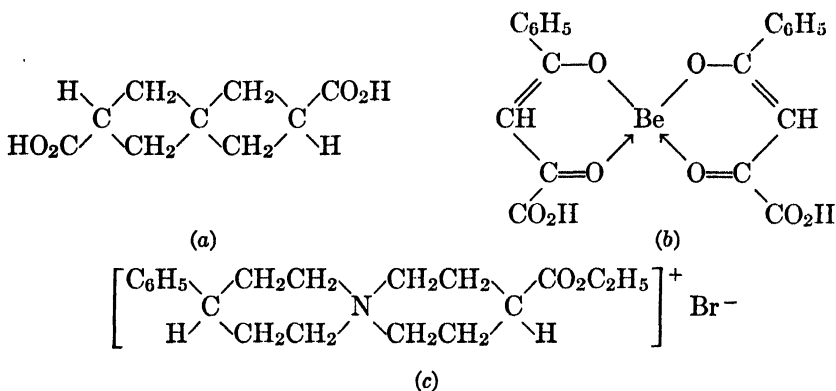
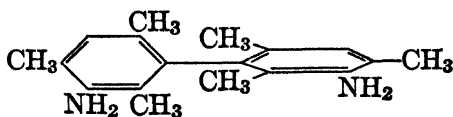


Figure *a* represents a spiran which differs from an allene in that the rings are four- rather than two-membered.

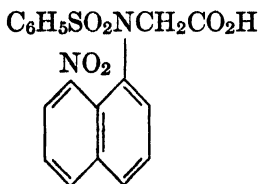
The chelated beryllium derivative of benzoylpyruvic acid is represented by figure *b*. The fact that this molecule is optically active is a proof of the reality of chelation.

The quaternary ammonium salt represented by figure *c* is also a resolvable spiran; this proves that the nitrogen atom in this molecule is tetrahedral.

**Substituted Biphenyls and Related Compounds.** Restricted rotation about the central bond in certain substituted biphenyls may also cause molecular asymmetry. The following is an example.



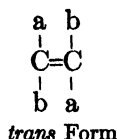
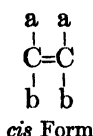
Such molecules are asymmetric only when each ring is unsymmetrically substituted. A similar case has been observed in the naphthalene series.



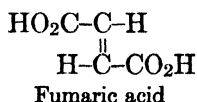
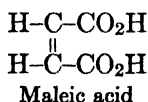
Here the free rotation about the amido nitrogen atom is prevented by the interference of the nitro group. The possibility that this molecule owes

its activity to the amido nitrogen atom seems remote. As yet it has not been possible to resolve a molecule of the type  $RR'R''N$ . Moreover, if the nitro group in the above molecule is replaced by a hydrogen atom the asymmetry is lost.

**cis-trans Isomerism.** *cis-trans* Isomerism (p. 146) may occur in a molecule having a structure so rigid that its parts are not free to rotate with respect to each other. The simplest type includes all olefins having the structure  $abC=Cab$ . This structure may exist in two forms known as *cis* and *trans*.

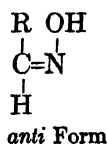
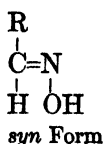


The best-known examples of this type of isomerism are maleic and fumaric acids.

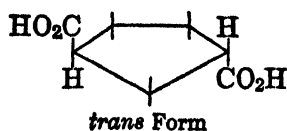
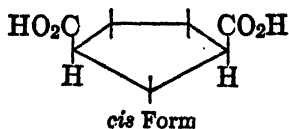


In fact, *cis* and *trans* forms are often called, respectively, *malenoid* and *fumaroid*. In general, the *cis* form is lower melting and more soluble than the corresponding *trans* form. For example, maleic acid melts at  $130^\circ$  whereas fumaric acid sublimates at  $286^\circ$ . Also, maleic acid is 100 times as soluble in water as is fumaric acid.

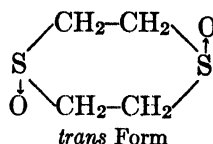
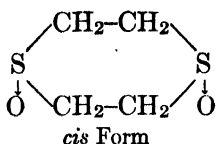
Oximes and many similar types of nitrogen compounds also may exist in *cis* and *trans* forms. These are often called, respectively, *syn* and *anti* forms.



*cis-trans* Isomerism may also occur in ring compounds in which the rigidity of the ring structure serves to prevent rotation. 1,3-Cyclopentanedicarboxylic acids illustrate this type.

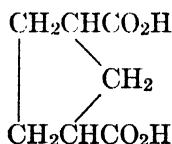


An extremely significant example of this type is presented by the disulfoxide of dithiane. Its two forms are represented below.



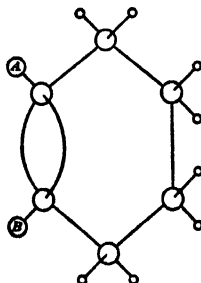
The existence of these forms shows that the three bonds of trivalent sulfur do not lie in one plane.

Cyclic compounds of the above type may exhibit both *cis-trans* and optical isomerism if asymmetric atoms are present. For example, 1,3-cyclopentanedicarboxylic acid has two similar asymmetric carbon atoms and should exist in a racemic and meso form (p. 168).



Because of the rigidity of the ring structure, it should exist in *cis* and *trans* forms. The *cis* form has a plane of symmetry and, thus, is the meso form; the *trans* acid is racemic (p. 220).

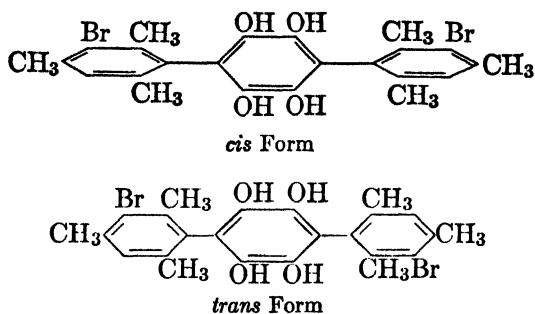
It is to be noted that *cis-trans* isomerism *due to a double bond* is not possible when the double bond is part of a ring system. This is evident from a consideration of a model of a 1,2-disubstituted-1-cyclohexene.



The groups A and B are in the plane of the ring.

Free rotation about a single bond is sometimes difficult or impossible because of the interference of the rotating parts. Thus, as we have already seen, biphenyl derivatives which have substituents in positions ortho to the central linkage may be incapable of rotation about this

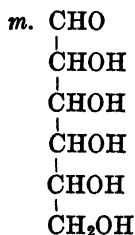
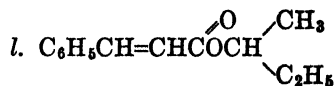
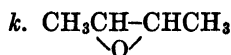
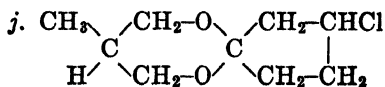
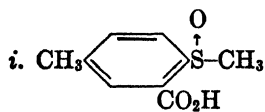
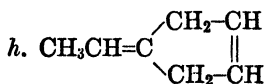
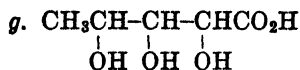
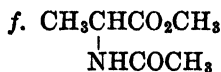
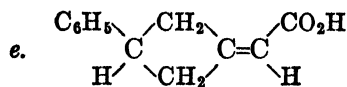
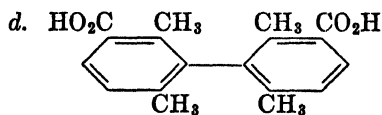
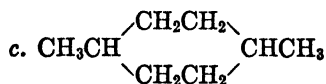
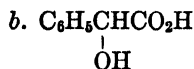
bond. This may give rise to geometrical isomerism as well as optical isomerism. An example is shown below.

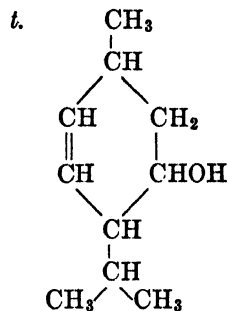
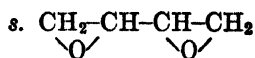
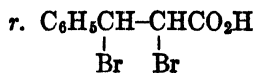
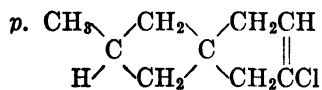
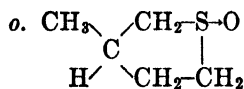
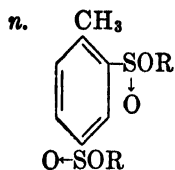


In this case neither form is capable of optical activity; the *cis* form has a plane of symmetry and the *trans* form has a center of symmetry.

### PROBLEM

Indicate the number and type of stereoisomers to be expected of the following structures.





## SUGGESTED READING

SHRINER, ADAMS, and MARVEL, "Stereoisomerism," Gilman's *Organic Chemistry* Chapter 3, p. 150. John Wiley and Sons, New York, 1938.

## CHAPTER XVIII

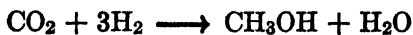
### INDUSTRIAL ALCOHOLS

Twenty years ago the only alcohols that were obtainable in quantity were methyl alcohol, made by the distillation of wood, and ethyl alcohol, obtained by fermentation of sugar with yeast. A by-product of the latter process was fusel oil, which consists of a mixture of amyl alcohols. No dihydroxy alcohol was on the market, and glycerol was the only polyhydroxy alcohol that was relatively cheap. Today the alcohols available commercially number more than a score. This is probably the most important advance which modern industrial chemists have made. For not only are these alcohols adapted to a wide variety of uses but they also serve as raw materials for the synthesis of a vast and imposing array of useful derivatives. Ethers, esters, acids, aldehydes, and ketones in great variety are available from the new inexpensive alcohols.

The events which led up to the manufacture of "higher alcohols" are absorbing. Probably the war-time (1914-1918) demand for acetone paved the way for the most important of these, for it nurtured the development of Weizmann's fermentation of starch (p. 49) to give acetone. This change is brought about by the bacterium *Clostridium acetobutylicum*. The organic products are acetone (30 per cent), ethyl alcohol (10 per cent), and *n*-butyl alcohol (60 per cent). In the large-scale manufacture of acetone, accordingly, vast quantities of *n*-butyl alcohol were made.

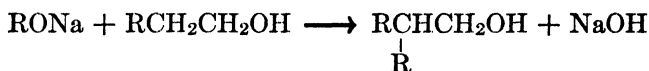
The story of *n*-butyl alcohol is one of the most interesting in the annals of the science. This little-known and apparently useless by-product proved to be the foundation stone for the modern lacquer industry. For a long time the Weizmann process was operated to produce the alcohol, and the ketone was regarded as a by-product. However, in 1941 the demand for acetone (as a solvent for processing cellulose nitrate) had increased so sharply that this may again be considered the more desirable of the two products.

Another product of Weizmann's fermentation is a gas which contains carbon dioxide (55 per cent) and hydrogen (45 per cent). This too has found a use. Part of the carbon dioxide is removed and the residual mixture subjected to high temperature and pressure in the presence of a suitable catalyst. Methanol is formed.



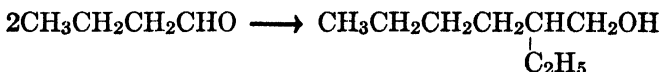
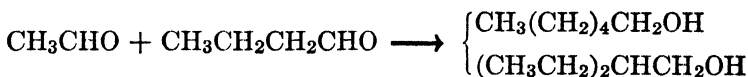
However, the importance of this synthesis of methanol is relatively insignificant when compared to that based on the hydrogenation of carbon monoxide. The latter process has made methanol as cheap as ethyl alcohol. It consists in the treatment of carbon monoxide with hydrogen in the presence of a zinc chromite catalyst at about 450° and 3000 lb. pressure.

By changes in the catalyst the methanol synthesis may be made to give a variety of higher alcohols. It is possible that the higher alcohols are derived from the lower ones by a condensation similar to the Guerbet reaction which is also a high-pressure process and consists in the interaction of an alcohol with an alcoholate.



Another method of making alcohols is hydration of olefins. The latter are available in vast amounts from the petroleum industry and yield an extensive collection of alcohols. Except for ethyl alcohol these are all secondary or tertiary alcohols.

The Carbide and Carbon Chemicals Corporation produces a series of alcohols which appear to be derived from acetaldehyde by condensation and hydrogenation.



The Sharples Corporation makes certain amyl alcohols from pentanes by chlorination and hydrolysis of the chloropentanes.

The most important alcohols which are commercially available are listed in Table XXV. The sources of the alcohols are indicated by the following abbreviations.

*O* = hydration of olefins

*G* = Guerbet reaction

*C* = Carbide and Carbon Chemicals Corporation's method

*F* = fermentation

*H* = hydrolysis of the corresponding chlorides

*P* = from carbon monoxide



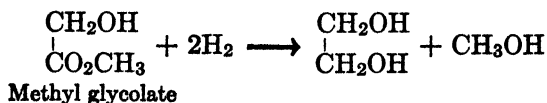
TABLE XXV

## INDUSTRIAL ALCOHOLS

Methanol	CH <sub>3</sub> OH	<i>P</i>
Ethanol	CH <sub>3</sub> CH <sub>2</sub> OH	<i>F O P</i>
1-Propanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<i>P</i>
2-Propanol	(CH <sub>3</sub> ) <sub>2</sub> CHOH	<i>O</i>
1-Butanol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> OH	<i>F</i>
2-Butanol	CH <sub>3</sub> CH <sub>2</sub> CHCH <sub>3</sub>   OH	<i>O</i>
Isobutyl alcohol	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> OH	<i>P</i>
<i>t</i> -Butyl alcohol	(CH <sub>3</sub> ) <sub>3</sub> COH	<i>O</i>
<i>n</i> -Amyl alcohol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> OH	<i>H</i>
2-Methyl-1-butanol	CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> OH	<i>F P H</i>
Isoamyl alcohol	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> OH	<i>F H</i>
2-Pentanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH(OH)CH <sub>3</sub>	<i>O H</i>
3-Pentanol	(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CHOH	<i>H</i>
<i>t</i> -Amyl alcohol	(CH <sub>3</sub> ) <sub>2</sub> C(OH)CH <sub>2</sub> CH <sub>3</sub>	<i>O</i>
<i>n</i> -Hexyl alcohol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> OH	<i>C</i>
2-Methyl-1-pentanol	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> OH	<i>P G</i>
2-Ethyl-1-butanol	(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> CHCH <sub>2</sub> OH	<i>C</i>
4-Methyl-2-pentanol	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH(OH)CH <sub>3</sub> (Hydrogenation of mesityl oxide?)	
1-Heptanol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>2</sub> OH (Hydrogenation of <i>n</i> -heptaldehyde)	
Diisopropylcarbinol	(CH <sub>3</sub> ) <sub>2</sub> CHCH(OH)CH(CH <sub>3</sub> ) <sub>2</sub>	<i>P</i>
2,4-Dimethyl-1-pentanol	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> OH	<i>P</i>
4-Methyl-1-hexanol	CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<i>P</i>
2-Octanol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH(OH)CH <sub>3</sub> (From castor oil)	
2-Ethyl-1-hexanol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub> OH	<i>C G?</i>
Lauryl alcohol	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> OH	
Palmityl alcohol (cetyl alcohol)	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> CH <sub>2</sub> OH	

By the catalytic hydrogenation of fats, lauryl, myristyl, palmityl, and stearyl alcohols are made. These are important because the sodium alkylsulfates (RCH<sub>2</sub>OSO<sub>3</sub>Na) derived from them are excellent detergents (p. 108). Cyclohexanol is made by catalytic hydrogenation of phenol.

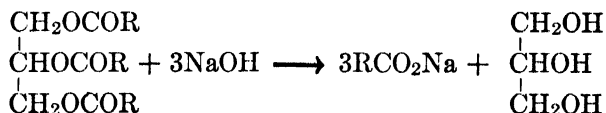
A hydrogenation process has also been developed for the production of ethylene glycol from methyl glycolate.



The most interesting feature of this method is the high-pressure synthesis of the glycolic ester. It is accomplished by condensation of carbon monoxide, formaldehyde, and methanol.



Glycerol as stated earlier (p. 58) has long been available as a by-product of soap manufacture.



Much of the supply is converted into glyceryl trinitrate or "nitroglycerine" (p. 58) which is used extensively as an explosive. This fact makes glycerol exceedingly important in war-time. During World War I a fermentation method was developed to meet the excessive demand for glycerol. A maximum yield is obtained when the fermentation is conducted within the pH range of 7.0 to 8.8. Ethyl alcohol, on the other hand, is formed in a markedly acid medium with a pH approaching 4.5.

At best, the production of glycerol from sugar can only be a war-time expedient for the cost is great. Recently a very promising method has been announced which involves the chlorination of propylene to give allyl chloride (p. 231). The latter may be converted to glycerol through glycerol  $\alpha,\gamma$ -dichlorohydrin.

About one-fourth of the annual output of glycerol is used in dynamite. Enormous amounts also go into the tobacco industry; glycerol is added to tobacco as a softening agent and to facilitate the maintenance of a given moisture content as well as to give sweetness and improved flavor.

Paints, varnishes, lacquers, and molded plastics require large amounts of glycerol. The manufacture of viscose uses about 20,000,000 lb. of glycerol annually.

### PROBLEMS

1. Make a list of the more important derivatives of (a) ethylene, (b) acetylene.
2. What important organic compounds can be made from castor oil?
3. What influence has the use of high-pressure technic had on the development of organic chemistry?

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 WILLIAMS, "Modern Petroleum Research," *Ind. Eng. Chem., News Ed.*, **16**, 630 (1938).

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## PART II

### CHAPTER XIX

#### ORGANIC HALOGEN COMPOUNDS

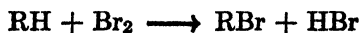
##### The Synthesis of Organic Halogen Compounds

The most useful methods available for the introduction of halogen atoms into organic molecules fall into three categories. These are halogenation, addition of a halogen or a halogen acid to an unsaturated group, and replacement of other functional groups. The methods will be considered in the order of mention.

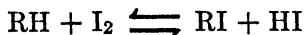
##### Halogenation

The direct replacement of a hydrogen atom by a halogen atom is known as *halogenation*. It is the only substitution reaction which is entirely general. Any hydrogen atom attached to a carbon atom may be replaced by a halogen atom. The ease with which this occurs varies, however, through an exceedingly wide range. The strength of the carbon-hydrogen linkage is greatly affected by the other atoms or groups of atoms which the carbon atom holds. Thus the replacement of the hydrogen atom by halogen may be very difficult, as with the paraffin hydrocarbons, or it may be extremely rapid, as with phenol and aniline. Moreover, all intermediate degrees of reactivity are encountered. On account of these differences it will be advantageous to discuss the different classes of organic compounds separately.

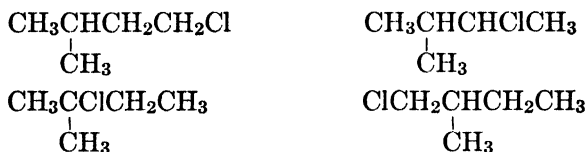
**Aliphatic Hydrocarbons.** The halogenation process which is most refractory is the direct halogenation of paraffins. The process is catalyzed by light and proceeds rapidly only at high temperatures. Under these conditions chlorination and bromination take place and yield the corresponding halogenation products along with a halogen acid.



Iodination, however, cannot be effected in this way; the reaction is reversible and the equilibrium lies far to the left.



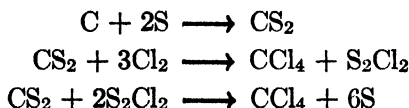
Direct chlorination or bromination of paraffins is seldom used to prepare the corresponding alkyl halides. This is because the reaction is difficult to control and invariably yields a mixture. Isopentane, for example, may yield four monochloro derivatives.



These in turn yield dichloro and polychloro derivatives so that the number of possible products is very large.

A commercial method (Sharples) has been developed for controlling the chlorination of a mixture of pentanes so that the product consists largely of monochloro pentanes. These are converted by hydrolysis to the corresponding alcohols. This process is important because, whereas the mixture of chlorides is a poor solvent, the mixture of amyl alcohols, known as Pentasol, is a good solvent. Pentacetate, a mixture of acetates made from Pentasol, is used as a solvent for lacquers.

It might be supposed that complete halogenation would be useful since it gives a single substance. Thus, carbon tetrachloride can be made by exhaustive chlorination of methane. However, the method is not used. Carbon tetrachloride is prepared industrially from the elements by the use of sulfur compounds.



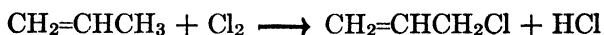
Fluorination is generally unsuccessful because the reaction proceeds with such violence as to produce fundamental disruption of the hydrocarbon molecule. Alkyl and aryl fluorides are produced by indirect methods to be mentioned later.

Certain generalizations can be made concerning the chlorination of saturated hydrocarbons in the absence of catalysts. One is that the replacement of a tertiary hydrogen atom\* is easier than that of a second-

\* It is customary to use the terms primary, secondary, tertiary, and quaternary to designate carbon atoms which are attached, respectively, to one, two, three, or four other carbon atoms. In turn, hydrogen atoms are referred to as primary, secondary, or tertiary depending on whether they are attached, respectively, to a primary, secondary, or tertiary carbon atom.

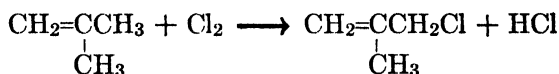
ary hydrogen atom which in turn can be replaced more readily than a primary hydrogen atom. At 300° the process is selective; the relative rates are primary, 1.00; secondary, 3.25; tertiary, 4.43. As the temperature is raised these ratios approach the values 1 to 1 to 1; i.e., at higher temperatures replacement tends to become purely random. It has also been observed that when a second chlorine atom enters the molecule it does not attach itself to the carbon atom which already holds a chlorine atom.

The chlorination of olefins has been found to take place readily under suitable conditions. The most important reaction of this type is the conversion of propylene to allyl chloride.

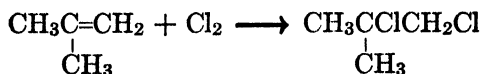


At 300° the reaction between chlorine and propylene is limited almost entirely to substitution, and yields of 80 per cent of the theory are obtained. The importance of this discovery lies chiefly in the fact that allyl chloride can be used as a starting point for the synthesis of glycerol.

Isobutylene is much more readily chlorinated than is propylene. It undergoes chlorination when the hydrocarbon and chlorine are brought together in the absence of light.



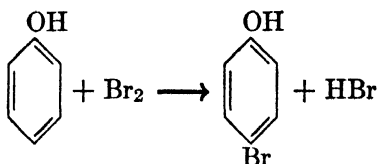
The reaction takes place rapidly in liquid films and on solid surfaces. By reducing the time of contact of the hydrogen chloride with the reaction product and with the excess isobutylene, the formation of by-products is minimized and good yields of methallyl chloride are obtained. The reaction is not greatly affected by temperature, but light causes reaction in the vapor phase resulting in the formation of the saturated dichloride instead of methallyl chloride.



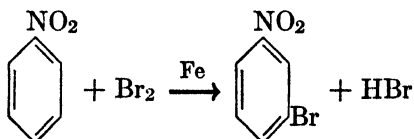
**Aromatic Compounds.** The mechanism of the halogenation process with aliphatic hydrocarbons is not known, and only conjectures are at hand as to the nature of the corresponding reaction in the aromatic series. But it seems certain that the two processes are fundamentally different in type. Whereas the halogenation of paraffins is promoted by heat and light, aromatic hydrocarbons require very different treatment. They react with the halogens in the presence of certain catalysts—known as “carriers”—of which iron is by far the most useful. Moreover, the reac-

tion takes place at relatively low temperatures and can be carried out in a controllable fashion.

*Meta* directing groups such as  $\text{NO}_2$ ,  $\text{CO}_2\text{H}$ ,  $\text{SO}_3\text{H}$ , and  $\text{COR}$  make the benzene ring less reactive whereas most of the *ortho-para* directing groups sensitize the ring. Thus, benzene derivatives in which the ring holds hydroxyl or amino groups react very readily with bromine and chlorine. Phenol, for example, is brominated rapidly at  $0^\circ$  without a catalyst to form *p*-bromophenol.



On the other hand, the bromination of nitrobenzene requires a high temperature and a catalyst. In the presence of iron and at a temperature of  $135\text{--}145^\circ$  a 60 to 75 per cent yield of *m*-bromonitrobenzene is obtained.

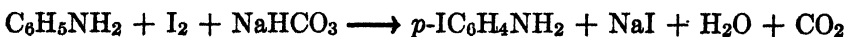


Direct iodination is also frequently used in the aromatic series. Nitric acid, mercuric oxide, ferric chloride, and other oxidizing agents are used to destroy the hydrogen iodide, thus permitting the reversible reaction to proceed. For example, iodobenzene is made by allowing benzene to react with iodine in the presence of nitric acid.



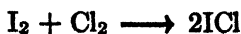
The nitric acid oxidizes hydrogen iodide to iodine.

Similarly, *p*-iodoaniline is formed when aniline reacts with iodine in the presence of sodium bicarbonate. In this instance the molecule is sensitive to oxidizing agents and hydrogen iodide is removed by the bicarbonate.

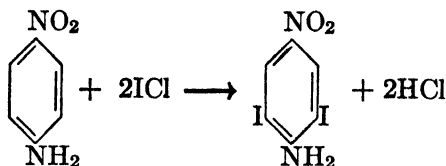


It will be noted that in this procedure only half of the iodine appears in the organic product.

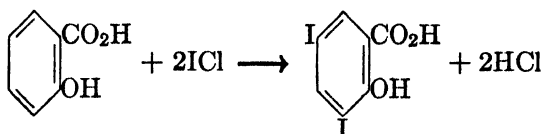
Another device for introducing iodine involves the use of iodine chloride. This reagent is made by adding chlorine to an equimolecular amount of iodine.



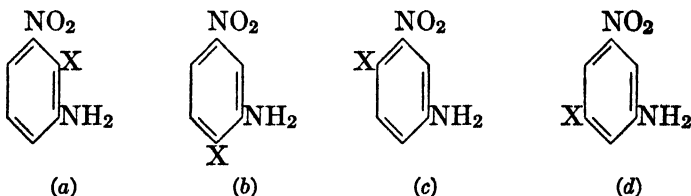
Iodine chloride reacts with *p*-nitroaniline to give the diiodo derivative.



Similarly, salicylic acid yields a diiodo derivative.



It is to be noted that when a hydroxyl or amino group is present it determines the orientation of the derivative. For example, halogenation of *m*-nitroaniline gives derivatives (*a*, *b*, and *c*) in which halogen atoms occupy positions *ortho* or *para* to the amino group. The *meta* directing influence of the nitro group is so small in comparison that practically none of the 1,3,5-derivative (*d*) is formed.



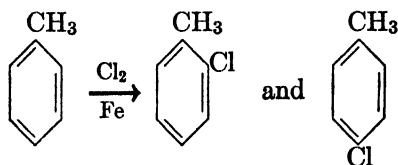
The solvents most frequently used for halogenation are chloroform and carbon tetrachloride. They dissolve the halogens as well as a wide variety of organic compounds but only small amounts of the halogen acids.

Many hydrocarbons contain aliphatic radicals joined to aromatic rings. Such radicals are known as side chains and the compounds are spoken of as mixed hydrocarbons. Halogenation of such substances usually can be made to proceed exclusively in the ring or in the side chain by proper control of conditions. The presence of iron as a "carrier" favors nuclear halogenation whereas heat and light in the absence of the carrier cause side-chain halogenation. Thus at high temperatures toluene may be chlorinated to give benzyl chloride, benzal chloride, or benzotrichloride.





In the presence of iron, however, it yields a mixture of *o*- and *p*-chloro-toluenes.



From a practical standpoint a reaction of this type is objectionable because it gives a mixture. The isomers are frequently hard to separate and neither can be obtained in high yield. In the majority of instances the boiling points of the *ortho* and *para* isomers lie close together, the *ortho* compound having the lower boiling point. Fractional distillation is, therefore, difficult. However, the melting point of the *para* isomer is generally much higher than that of the *ortho* derivative. It often happens that the *para* compound will crystallize and can be separated from the *ortho* isomer by filtration. Table XXVI contains the melting and boiling points of some *ortho* and *para* compounds.

TABLE XXVI

BOILING POINTS AND MELTING POINTS OF SOME *ortho* AND *para* DISUBSTITUTED BENZENE DERIVATIVES

Substituents	<i>Ortho</i>		<i>Para</i>	
	b.p.	m.p.	b.p.	m.p.
CH <sub>3</sub> , Cl	159°	-34°	162°	7.5°
CH <sub>3</sub> , Br	182	-28	185	28.5
CH <sub>3</sub> , NO <sub>2</sub>	222	-11	238	51.9
CH <sub>3</sub> , NH <sub>2</sub>	200	-16	200	45
CH <sub>3</sub> , OH	191	31	202	36
OH, Cl	176	7	217	41
OH, Br	195	0	238	63.5
OH, NO <sub>2</sub>	214	5.6	...	114
NO <sub>2</sub> , Cl	246	45	242	84
NO <sub>2</sub> , Br	261	33	256	127
CH <sub>3</sub> O, Cl	195	43	200	127
CH <sub>3</sub> O, Br	221	..	215	...
CH <sub>3</sub> O, NO <sub>2</sub>	272	..	274	13
		9		54

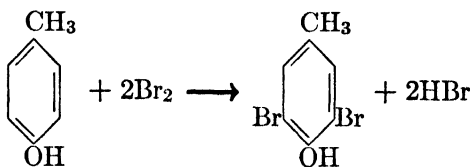
It is interesting to note that the methyl group in toluene is much more reactive than that in a paraffin hydrocarbon. The phenyl group ex-

dently activates the hydrogen atoms on the carbon atom joined to the benzene ring. This effect, however, is not appreciable at points farther along a side chain. For example, *n*-propylbenzene will take up two chlorine atoms readily, and both are found on the  $\alpha$ -carbon atom.

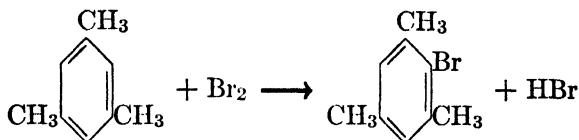


The remaining hydrogen atoms of the side chain possess a reactivity similar to that of paraffin hydrocarbons.

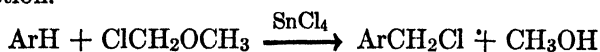
Side-chain halogenation is difficult or impossible if the ring holds sensitizing groups such as hydroxyl or amino. Thus, even in the absence of a carrier, *p*-cresol reacts rapidly with bromine to form the dibromo derivative.



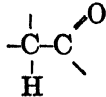
The presence of alkyl groups on the ring facilitates halogenation. Mesitylene undergoes nuclear substitution almost exclusively when treated with bromine even in the absence of catalysts.



An alternate method for the introduction of the  $-\text{CH}_2\text{Cl}$  group consists in the treatment of an aromatic hydrocarbon with chloromethyl ether in the presence of stannic chloride. The process is known as chloromethylation.

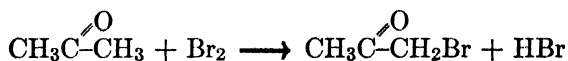


The same result is achieved by using a mixture of paraformaldehyde and hydrochloric acid. The halogen atoms can be removed by hydrogenation; this is used as a method of methylation. Mesitylene and anisole, for example, have been progressively methylated to hexamethylbenzene and pentamethylanisole, respectively.

**Carbonyl Compounds.** Compounds which contain the group  can generally be halogenated easily to give monohalogen derivatives. This includes aldehydes and ketones, as well as acids and

their derivatives. This type of halogenation is extremely useful in synthesis. The ease with which the reaction proceeds varies considerably and depends on the nature of the other groups in the molecule.

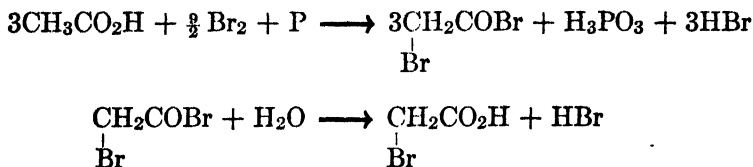
The bromination of acetone has been studied extensively and will serve as an illustration of this type of halogenation.



The remarkable ease with which this type of compound undergoes bromination is due to the activating effect of the carbonyl group and is more or less proportional to the reactivity of this group. This is in keeping with the fact that the halogen atom always replaces a hydrogen atom on the  $\alpha$ -carbon atom. If there is no  $\alpha$ -hydrogen atom halogenation takes place no more readily than it does with saturated aliphatic hydrocarbons (p. 12).

The only carbonyl compounds in which halogenation proceeds with difficulty are the acids. Even though an acid may contain one or more  $\alpha$ -hydrogen atoms it will react only slowly with chlorine or bromine and not at all with iodine. This accords with the earlier observation (p. 89) that the carboxylic acids exist as chelated dimers and, thus, have no true carbonyl group.

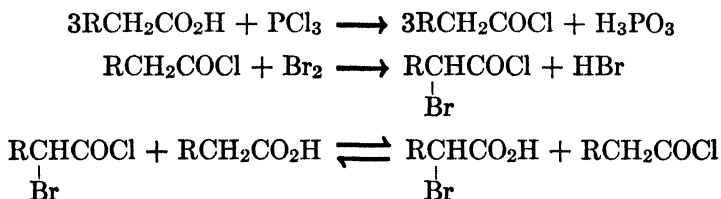
In many acid derivatives such as acid chlorides and anhydrides resonance effects are less pronounced, and these substances can be halogenated with comparative ease. Methods for halogenating acids generally involve catalysts which produce the acid chlorides or anhydrides as intermediates. The classical procedure for doing this is to treat the acid with red phosphorus and chlorine or bromine and then water. In the bromination of acetic acid, for example, the reactions involved are the following:



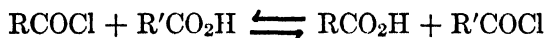
This is known as the Hell-Volhard-Zelinsky method.

More recently it has been recognized that the same result may be attained by use of a trace of a phosphorus trihalide as a catalyst. This produces some acid halide which is then halogenated and in turn reacts with unchanged acid to give more acid halide. The reactions involved

in the bromination of an acid in the presence of a trace of phosphorus trichloride are as follows:

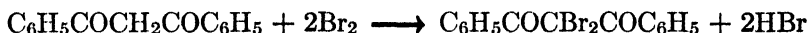


From these equations it is clear that only catalytic amounts of phosphorus trichloride are needed. This mechanism is supported by the fact that acid chlorides are known to form equilibrium mixtures with acids.

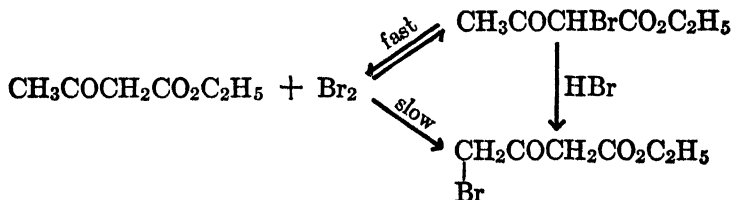


It seems altogether probable then that in the Hell-Volhard-Zelinsky and other methods for halogenating acids operation is really on acid chlorides or anhydrides.\*

Compounds which have a methylene ( $\text{CH}_2$ ) or methinyl ( $\text{CH}$ ) group between two carbonyl groups have a great tendency to enolize and consequently are very easily halogenated. Dibenzoylmethane, for example, absorbs bromine very rapidly to give a dibromide.



Similarly ethyl acetoacetate yields the  $\alpha$ -bromo derivative. It is particularly interesting that dry hydrogen bromide converts this ester to the corresponding  $\gamma$ -bromo derivative. Presumably the  $\alpha$ -isomer reacts with hydrogen bromide to give bromine which replaces a  $\gamma$ -hydrogen atom.



Iodination of enolic compounds can be effected by treatment with iodine using hydrogen peroxide to remove the hydrogen iodide. Ethyl

\* It should be pointed out that acid chlorides are themselves really acid anhydrides. Acetyl chloride, for example, is a mixed anhydride of acetic and hydrochloric acids. This explains the observation that acid chlorides and acid anhydrides have very similar chemical properties.

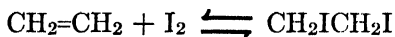
$\alpha$ -iodoacetoacetate is obtained in 90 per cent yields from ethyl acetoacetate.

### Addition

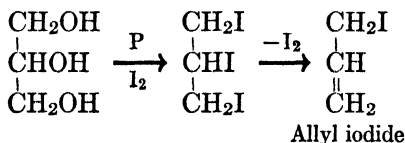
**Olefins and Acetylenes.** Chlorine and bromine react additively with olefins to form dihalogen compounds.



Chlorine enters into this type of reaction more readily than does bromine; iodine shows little tendency to combine with olefinic compounds. In fact, compounds in which two iodine atoms are held on adjacent carbon atoms tend to decompose into iodine and olefinic molecules. Ethylene iodide, for example, forms when ethylene is passed into an alcoholic solution of iodine. If allowed to stand in the open it slowly disappears because of spontaneous dissociation into ethylene and iodine.



The synthesis of allyl iodide from glycerol, red phosphorus, and iodine apparently depends on this phenomenon. The normal product, 1,2,3-triiodopropane, evidently loses iodine to give allyl iodide.

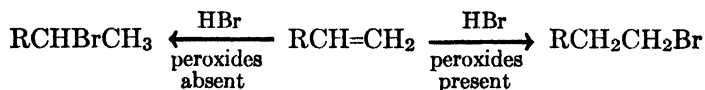


However, iodine chloride can be added to olefinic linkages. Both the Hübl and the Wijs methods for determining the iodine number of fats depend on this reaction. In the former a chloroform solution of iodine and mercuric chloride is employed and in the latter a solution of iodine and iodine chloride is used. In these procedures iodine chloride rather than iodine is added to the double bonds.

The addition of halogen acids to olefinic compounds is not much used as a method of preparing halogen compounds. The most important example is the addition of hydrogen chloride to ethylene to give ethyl chloride. This is carried out commercially by the use of bismuth trichloride as a catalyst. It is important primarily because of the use of ethyl chloride in the synthesis of tetraethyl lead.

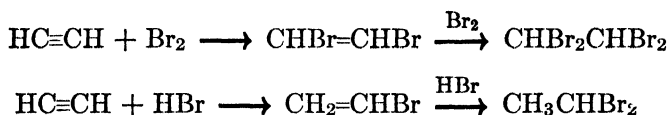
The addition of halogen acids generally follows Markownikoff's rule, the halogen atom going to the carbon atom holding the fewer hydrogen atoms. It has been found, however, that the addition of hydrogen bromide takes place in the reverse sense if peroxides are present. This is known as the "peroxide effect" and has been observed with such com-

pounds as allyl bromide, vinyl bromide, propylene, and isobutylene; the double bond in every case involves a terminal carbon atom.



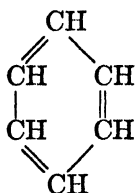
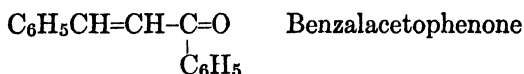
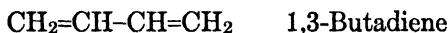
The mode of addition of other hydrogen halides does not appear to be affected by peroxides.

The addition of halogens and halogen acids to acetylene leads to a number of important derivatives of ethylene and ethane.



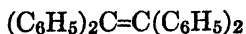
It is to be noted that in the addition of hydrogen bromide to vinyl bromide, ethylidene and not ethylene bromide is formed. This is in accord with Markownikoff's rule.

**Conjugated Systems.** A compound which has double bonds alternating with single bonds is said to be conjugated or to possess a conjugated system. Examples are 1,3-butadiene, benzalacetophenone, and benzene.

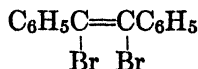


Benzene

Resonance is possible in all such systems and as a consequence they are less reactive than would be expected. The addition of halogens to benzene or benzalacetophenone, for example, is not rapid. Similarly, acrylic acid takes up bromine less readily than does ethylene. Olefinic linkages which are conjugated with several such groups or other negative atoms or groups have little or no tendency to react with halogens. Tetraphenylethylene and 1,2-dibromodiphenylethylene are examples.

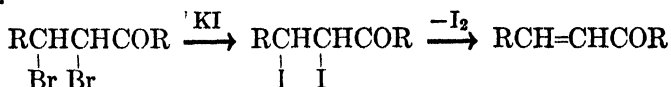


Tetraphenylethylene

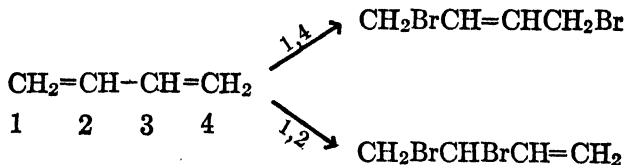


1,2-Dibromodiphenylethylene

The difference between bromine and iodine in this respect is well illustrated by Kohler's method of preparing  $\alpha,\beta$ -unsaturated ketones. The  $\alpha,\beta$ -dibromo compound is converted to the corresponding diiodo derivative by treatment with potassium iodide. The diiodo compound, however, breaks down spontaneously to give iodine and the unsaturated ketone.

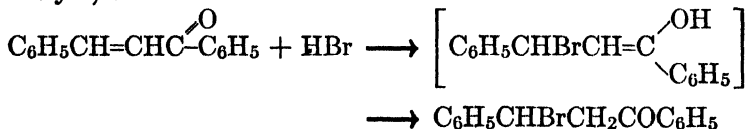


Additions to conjugated systems frequently occur in an anomalous manner. Bromine and butadiene, for instance, give principally 1,4-dibromo-2-butene instead of 1,2-dibromo-3-butene.

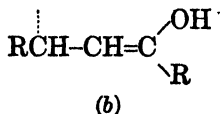
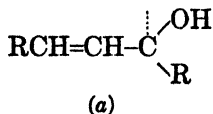


Similarly, 1,3-butadiene reacts with hydrogen chloride, hydrogen bromide, and hydrogen iodide. The yields of the corresponding crotyl halides are 52, 81, and 52 per cent, respectively.

This mode of reaction is known as 1,4 addition. When hydrogen bromide reacts with benzalacetophenone the addition is believed to be exclusively 1,4.



The unstable enol, whose formation is postulated as the first step in the process, rearranges at once to a bromo ketone. It seems probable that the driving force of the reaction is the tendency of the oxygen atom to coordinate with a proton. The resulting molecular fragment might have either of the following forms:



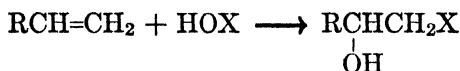
Form *a* offers an opportunity for the bromide ion to become attached to carbon atom 2, i.e., give 1,2 addition. Similarly form *b* gives the opportunity for 1,4 addition. However, the product of 1,2 addition would

be extremely unstable and revert almost entirely to the parent substances. This shows why the product is of the 1,4 type. It will be noted that this type of addition generally disregards Markownikoff's rule.

On the other hand, bromine reacts with  $\alpha,\beta$ -unsaturated carbonyl compounds in the 1,2 manner. This addition, however, is not as rapid as with olefins.

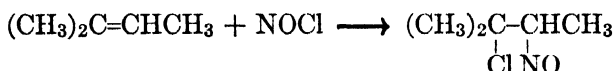
In general, 1,2 and 1,4 additions are competing reactions when conjugated systems are involved. The course of such reactions depends on many factors; these will be referred to frequently in subsequent sections.

**Hypohalous Acids.** Hypohalous acids can be caused to react additively with compounds containing ethylenic linkages:

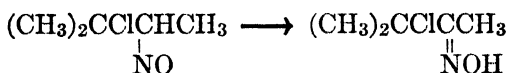


It is important to note that in this reaction the hydroxyl group appears to be the negative part of the hydrogen hypohalite molecule; it always attaches itself to the carbon atom which holds the fewer hydrogen atoms.

**Nitrosyl Chloride.** Nitrosyl chloride reacts additively with olefins to give nitrosochlorides. For example, trimethylethylene reacts as follows:



When heated or allowed to stand this nitrosochloride rearranges to the oxime.



The nitrosochlorides are usually solid and have been used extensively in characterization work, notably in the terpene series. To prepare them it is not necessary to make nitrosyl chloride; a mixture of ethyl or amyl nitrite with concentrated hydrochloric acid will serve the same purpose. In crystalline form they are dimeric and colorless. In solution or when melted they tend to revert to the monomers which are blue.

### Replacement of Functional Groups

Introduction of halogen atoms by direct halogenation has proved to be of little value in the aliphatic series and even in the aromatic field frequently gives mixtures (of *ortho* and *para* isomers, for example) or is inapplicable because of unfavorable orientation tendencies. The introduction of a halogen atom at a particular point in a molecule is often effected by replacement of some other functional group already present.



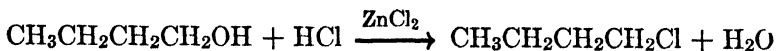
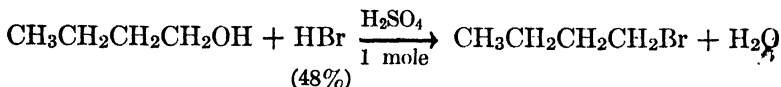
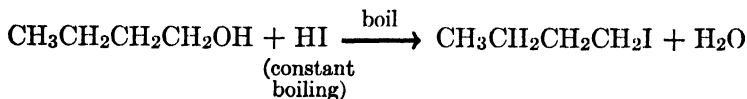
This is an especially valuable method in the aliphatic field where direct halogenation is of least value.

**Hydroxyl Groups.** Most compounds containing hydroxyl groups may be transformed into halogen derivatives by the use of hydrogen halides, phosphorus halides, or thionyl chloride. The three most important classes to be considered are alcohols, phenols, and carboxylic acids.

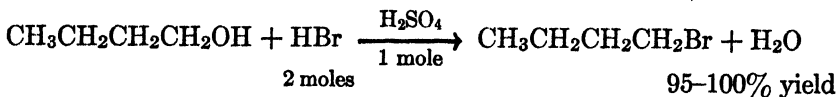
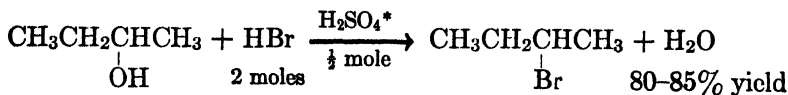
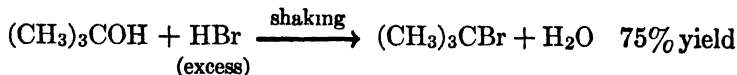
*Alcohols.* Alcohols react with hydrogen halides to give the corresponding alkyl halides.



This is a very general and useful reaction. However, the rate and the yield vary considerably with the nature of the reactants. Thus hydrogen iodide reacts more rapidly than does hydrogen bromide, which, in turn, reacts faster than does hydrogen chloride. The difference is illustrated by the conditions which are most favorable for the transformation of *n*-butyl alcohol into the corresponding halides.



In a given series the tertiary alcohols react fastest and the primary alcohols slowest, with the secondary alcohols taking an intermediate position. For example, the following butyl alcohols react with hydrogen bromide as indicated.



\* A mixture of hydrobromic and sulfuric acids is conveniently prepared by passing sulfur dioxide into bromine, ice, and water until the bromine color is discharged. The reaction is:  $\text{Br}_2 + \text{SO}_2 + 2\text{H}_2\text{O} \longrightarrow 2\text{HBr} + \text{H}_2\text{SO}_4$ . If an equimolecular mixture is desired, the calculated additional quantity of sulfuric acid is added.

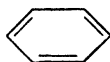
Although tertiary and secondary alcohols are more reactive than primary alcohols, they generally form the halides in lower yields because of loss through side reactions. The chief among these is dehydration to the corresponding olefin.

This difference in the rates at which alcohols react has been made the basis of the Lucas test, which was designed to distinguish between primary, secondary, and tertiary alcohols. The alcohol is shaken with a solution of zinc chloride in concentrated hydrochloric acid at room temperature. Under these conditions a tertiary alcohol reacts at once and the mixture becomes turbid due to the presence of the insoluble alkyl halide. Secondary alcohols react within five minutes; primary alcohols fail to give alkyl chlorides unless the mixture is heated or allowed to stand several hours.

There are some exceptions to the Lucas test, and among these allyl alcohol and benzyl alcohol deserve special mention. The presence of a double bond adjacent to the  $\text{CH}_2\text{OH}$  group renders the hydroxyl group unexpectedly reactive.

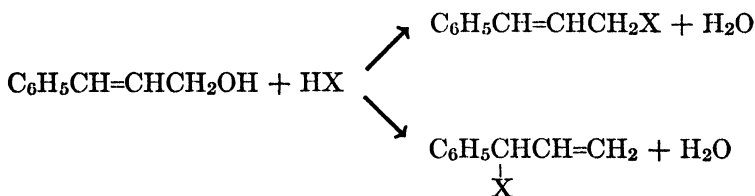


Allyl alcohol



Benzyl alcohol

Cinnamyl alcohol belongs to the same category. It reacts rapidly with hydrogen halides to give cinnamyl halides, but the isomeric 3-phenyl-3-halo-1-propenes are formed simultaneously.



The group  $\text{CH}=\text{CHCH}_2\text{OH}$  is an example of a triad system. Such systems generally lead to rearrangements of this type, known as allylic or 1,3 rearrangements. Doubtless allyl compounds also undergo this type of rearrangement, but the two products are identical.

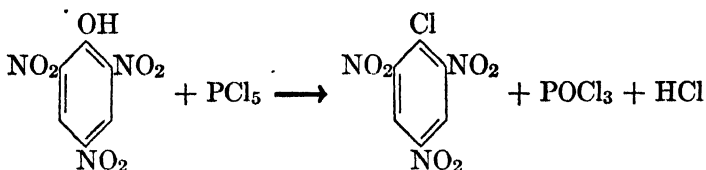
A very interesting reaction is observed with glycerol, which with hydrogen chloride gives the  $\alpha,\gamma$ -dichloro derivative, the primary alcohol groups reacting faster than the secondary.

Phosphorus trichloride or tribromide may be used in place of the corresponding hydrogen halide.



These reagents are generally about as good as the hydrogen halides but are less frequently used.

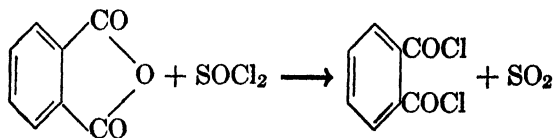
*Phenols.* Phenols sometimes react with phosphorus pentahalides to give low yields of aryl halides. The reaction is favored by the presence of nitro, carboxyl, and other *meta*-directing groups when *ortho* or *para* to the hydroxyl group. Picryl chloride, for example, can be made satisfactorily by the action of phosphorus pentachloride on picric acid.



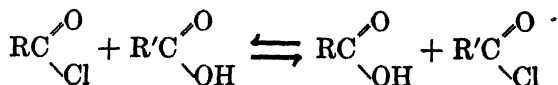
*Carboxylic Acids.* Carboxylic acids may be transformed into the corresponding acid halides by the action of thionyl or phosphorus halides (p. 95).

Since the acid chloride is rarely made for its own sake but generally as an intermediate in the transformation of the acid into other derivatives it is especially convenient to use thionyl chloride. The excess reagent is distilled and the residual acid chloride used directly for the next step in the synthesis.

Thionyl chloride cannot be used in all cases. It converts succinic, glutaric, and phthalic acids to the corresponding anhydrides, and it fails to attack oxalic, tartaric, fumaric, and terephthalic acids. However, the addition of small amounts of zinc chloride and the use of higher temperatures bring satisfactory results with phthalic, fumaric, and succinic acids. The preparation of phthalyl chloride in an 86 per cent yield is effected by treating the anhydride with thionyl chloride at 220° in the presence of traces of zinc chloride.



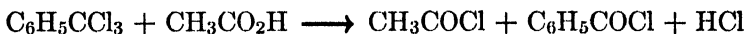
When an acid chloride is mixed with an organic acid the following equilibrium is set up.



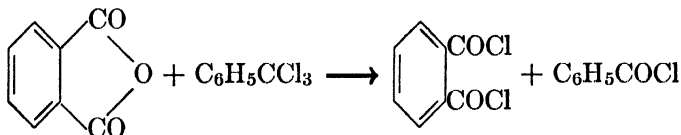
Advantage is taken of this to prepare more volatile acid chlorides from less volatile ones. Thus acetyl chloride is conveniently made by mixing

acetic acid and benzoyl chloride in equimolecular amounts and distilling the acetyl chloride (p. 95).

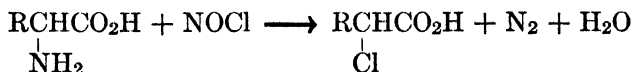
Benzotrichloride can be used in this way. When it is heated with acetic acid an equimolecular mixture of benzoyl chloride and acetyl chloride is formed.



The two acid chlorides are easily separated by distillation. Another example of the use of benzotrichloride is the conversion of phthalic anhydride to the chloride.

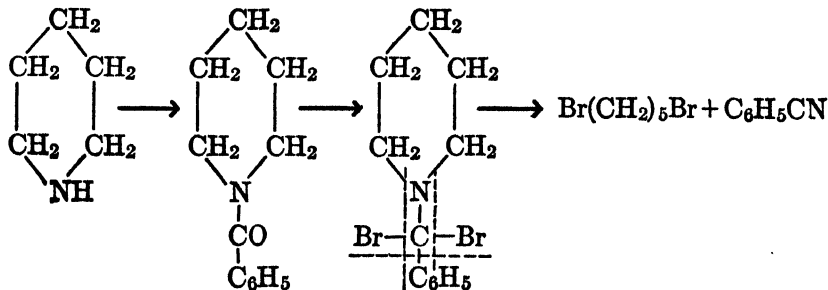


**The Amino Group.** Direct replacement of amino groups by halogen atoms is rarely possible. It may be accomplished with  $\alpha$ -amino acids by use of nitrosyl chloride or bromide.



It seems probable that an unstable diazo compound is formed as an intermediate. The reaction goes smoothly only when the amino group is in the *alpha* position.

An indirect method of great interest is due to von Braun. He was able to convert cyclic secondary amines into dibromo paraffins by transforming them into benzoyl derivatives and treating these with phosphorus pentabromide.\* In this way, for example, he made pentamethylene bromide from piperidine. The steps in this transformation are probably the following:

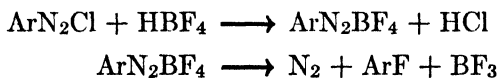


\* Phosphorus pentabromide is made by adding a mole of bromine to a mole of phosphorus tribromide. In the above example the tribromide and benzoylpiperidine are mixed in equimolecular proportions and to this mixture is added the theoretical amount of bromine.

**The Diazonium Group.** Primary aromatic amino groups may be replaced by halogen atoms indirectly by first converting them to the corresponding diazonium compounds (p. 119).

Decomposition of a diazonium salt in the presence of hydrogen iodide yields the corresponding iodo compound. For the replacement by chlorine or bromine either the Sandmeyer (p. 120) or Gattermann (p. 120) method is used.

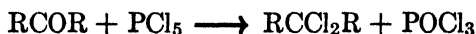
The introduction of fluorine atoms requires a special procedure. After the diazotization is complete fluoboric acid is added; this gives an insoluble borofluoride which is removed by filtration and dried. The dry salt is then decomposed thermally.



Another method involves the use of anhydrous liquid hydrogen fluoride, which has become available recently. The primary aromatic amine is dissolved in cold hydrogen fluoride and the solution is treated with sodium nitrite and allowed to stand until the hydrogen fluoride (b.p. 19.4°) has evaporated. The residue consists of the aryl fluoride and sodium fluoride.



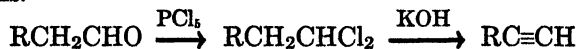
**The Carbonyl Group.** Aldehydes and ketones react with phosphorus pentahalides to give the corresponding dihalogen derivatives.



This reaction is much used to convert methyl aryl ketones to acetylenic compounds.

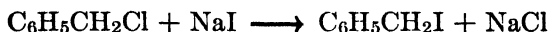


The first molecule of hydrogen chloride is easily eliminated, and the second can be removed by treatment with alcoholic potash. Aliphatic aldehydes yield 1,1-dichloro derivatives of the corresponding paraffins. Bourguet has shown that these can be dehydrohalogenated to acetylenic hydrocarbons.



**Halogen Atoms.** Bromine and chlorine atoms, if sufficiently active, may be replaced by iodine atoms by dissolving the organic halogen compound in acetone and adding sodium iodide. Sodium iodide is soluble

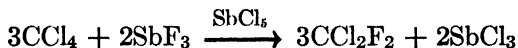
in acetone whereas sodium bromide and chloride are not. Benzyl iodide is made from benzyl chloride in this way.



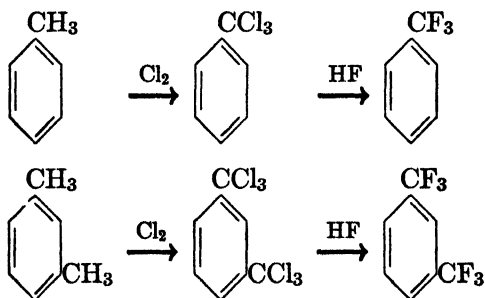
The speed of replacement of chlorine and bromine by this method varies with the nature of the radical to which the halogen atom is attached. By means of this reaction a method of wide applicability has been developed for comparing the reactivities of the halogen atoms in organic compounds.

It is probable that this replacement of chlorine or bromine by iodine is the cause of the catalytic effect of iodides on reactions which involve chlorine or bromine compounds.

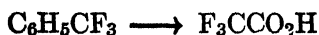
Fluorine atoms are commonly introduced by treating chlorine, bromine, or iodine compounds with antimony trifluoride. Antimony pentachloride is used as the catalyst. The important refrigerant, dichlorodifluoromethane, is made from carbon tetrachloride by this method.



This synthesis can be simplified and made considerably cheaper by the use of anhydrous hydrogen fluoride in place of antimony trifluoride. A catalyst is necessary in the aliphatic series. Aromatic trifluoromethyl compounds are made by chlorination of the methyl compound and replacement of the chlorine atoms with fluorine. Toluene and *m*-xylene for example yield, respectively, benzotrifluoride and *m*-di(trifluoromethyl)benzene.

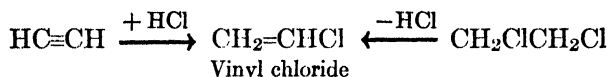


The trifluoromethyl group is exceedingly resistant to attack by reagents. Vigorous oxidation of benzotrifluoride, for instance, destroys the ring and yields trifluoroacetic acid.



### Other Halogen Compounds

Vinyl halides are generally made from dihalides by the elimination of a molecule of halogen acid or by the addition of a halogen acid to an acetylenic compound as noted earlier. The most important vinyl halide is vinyl chloride. It is made by adding hydrogen chloride to acetylene or removing it from ethylene chloride.



$\beta$ -Bromostyrene is generally made by boiling the dibromide of cinnamic acid with potassium acetate.



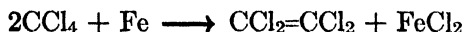
Chloroform, bromoform, and iodoform are easily made by the action of the corresponding hypohalite on ethyl alcohol or acetone (p. 81).



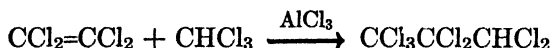
Chloroform is made industrially by reducing carbon tetrachloride with iron and water.



A by-product of this reaction is tetrachloroethylene.



Tetrachloroethylene can be condensed with chloroform in the presence of aluminum chloride to give heptachloropropane.



$\alpha$ -Halogen ethers may be made by treating aldehydes with alcohols and hydrogen chloride. From methanol, formaldehyde, and hydrogen chloride, chloromethyl ether is obtained.



## REACTIONS OF ORGANIC HALOGEN COMPOUNDS

### Alkyl Halides

Alkyl halides undergo a wide variety of reactions, most of which involve replacement of the halogen atom. They may be converted to alcohols by hydrolysis, to amines by treatment with ammonia, to nitriles by reaction with sodium cyanide, to mercaptans by the action of sodium

hydrosulfide, and to thio ethers through interaction with sodium sulfide. In spite of the multiplicity of such reactions only a few can be said to have practical value in synthetic work. Some of these will now be discussed briefly.

**The Wurtz Reaction.** Alkyl halides react with metallic sodium to form paraffins in yields of 50 per cent or better. For example, *n*-octane, *n*-decane, and *n*-octacosane are made in satisfactory yields from *n*-butyl, *n*-amyl, and myristyl bromides, respectively.

**The Grignard Reaction.** Alkyl halides in dry ether dissolve metallic magnesium to form Grignard reagents. These are of great value synthetically and will be discussed at length at a later point.

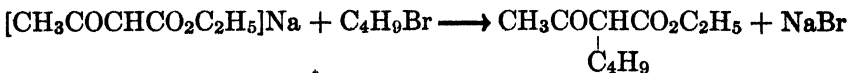
**The Formation of Nitriles.** Alkyl halides react with sodium cyanide to give nitriles. Good yields are possible only with primary halides; in these cases yields of eighty to ninety per cent are often obtained. Examples are benzyl chloride and *n*-butyl bromide, which produce, respectively, benzyl cyanide and valeronitrile.



**Alkyl Halides as Alkylating Agents.** The foregoing reaction is only one of many in which alkyl halides react with metal derivatives by metathesis, yielding alkyl derivatives. Another is the interaction of alkoxides and phenoxides with alkyl halides to give ethers. This is the Williamson synthesis (p. 54) and serves as a general method for making mixed ethers in which at least one radical is aliphatic. As an example may be cited the preparation of anisole from sodium phenoxide and methyl iodide.



A somewhat similar reaction is involved in the alkylation of active methylene compounds. Here, however, the alkyl group generally becomes attached to a carbon atom. An example is furnished by the interaction of *n*-butyl bromide and the sodium derivative of ethyl acetoacetate to give ethyl *n*-butylacetoacetate.

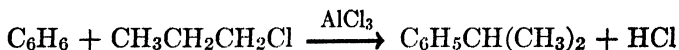


This important method will be discussed in detail in a later chapter.

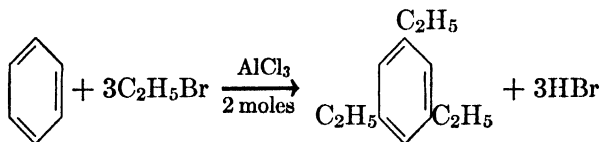
**The Friedel-Crafts Reaction.** A similar use is made of alkyl halides in preparing alkyl derivatives of aromatic hydrocarbons by the Friedel-Crafts method. The introduction of methyl, ethyl, or isopropyl groups offers no great difficulty, but the introduction of *n*-propyl or *n*-butyl



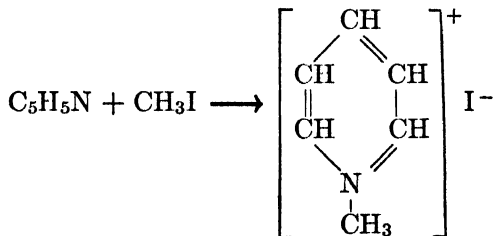
groups in this way is unsatisfactory. Rearrangement takes place to give chiefly the corresponding branched-chain alkyl derivatives. Thus, benzene and *n*-propyl chloride react in the presence of aluminum chloride to give isopropyl- rather than propylbenzene.



A remarkable feature of the alkylation of benzene by this method is that the alkyl groups take up the *meta* rather than *ortho-para* positions. Thus, benzene and ethyl bromide react to give 1,3,5-triethylbenzene.



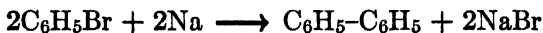
**Quaternary Ammonium Salts.** When a tertiary amine is allowed to react with an alkyl halide a quaternary ammonium salt is formed (p. 112). These are generally solids and are sometimes used in the identification of such amines. An example is the formation of the methiodide of pyridine.



The relative reactivities of alkyl halides as measured by the reaction with silver nitrate or in typical metatheses with alkali salts fall in the order  $\text{RI} > \text{RBr} > \text{RCl}$  and primary < secondary < tertiary.

### Aryl Halides

**The Wurtz-Fittig Reaction.** Aryl halides are comparatively inert toward most of the reagents listed for alkyl halides. Metals, however, attack them. Sodium is capable of coupling bromobenzene to give biphenyl.



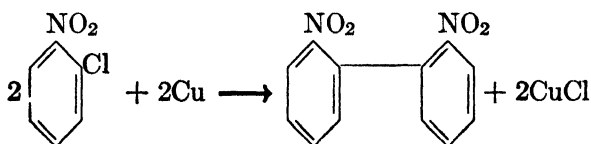
This is the Fittig reaction. Unlike the Wurtz method, it gives very low yields because of the many side reactions. A valuable method, however,

is obtained by combining these. It is known as the *Wurtz-Fittig reaction* and is useful for fixing aliphatic side chains on aromatic rings. For example, *n*-butylbenzene can be made in good yields by treating a mixture of bromobenzene and butyl bromide with sodium.

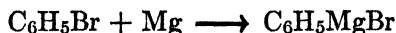
1.  $\text{C}_6\text{H}_5\text{Br} + 2\text{Na} \longrightarrow \text{C}_6\text{H}_5\text{Na} + \text{NaBr}$
2.  $\text{C}_6\text{H}_5\text{Na} + \text{C}_6\text{H}_5\text{Br} \longrightarrow \text{C}_6\text{H}_5\text{C}_6\text{H}_5 + \text{NaBr}$
3.  $\text{C}_4\text{H}_9\text{Br} + 2\text{Na} \longrightarrow \text{C}_4\text{H}_9\text{Na} + \text{NaBr}$
4.  $\text{C}_4\text{H}_9\text{Na} + \text{C}_4\text{H}_9\text{Br} \longrightarrow \text{C}_8\text{H}_{18} + \text{NaBr}$
5.  $\text{C}_4\text{H}_9\text{Na} + \text{C}_6\text{H}_5\text{Br} \longrightarrow \text{C}_6\text{H}_5\text{C}_4\text{H}_9 + \text{NaBr}$
6.  $\text{C}_6\text{H}_5\text{Na} + \text{C}_4\text{H}_9\text{Br} \longrightarrow \text{C}_6\text{H}_5\text{C}_4\text{H}_9 + \text{NaBr}$

This is probably to be accounted for by the foregoing equations. Reaction 1 would be expected to proceed more rapidly than 3, thus giving a preponderance of sodiumphenyl over sodiumbutyl. Consequently, reaction 6 would be favored over 4 (Wurtz) or 2 (Fittig).

**The Ullmann Method.** A useful modification of the Fittig reaction was developed by Ullmann who replaced sodium by copper powder. Yields as high as 80 per cent are obtained from aryl iodides; bromides and chlorides also give good yields if the halogen atom is situated in a position *ortho* or *para* to a nitro group. Thus from *o*-chloronitrobenzene a 60 per cent yield of 2,2'-dinitrobiphenyl results.



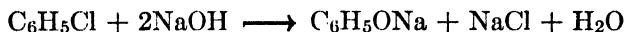
**The Grignard Reaction.** With metals, aryl halides undergo three generally useful reactions. In addition to the Wurtz-Fittig and Ullmann reactions already mentioned is the formation of Grignard reagents. This reaction is general for aryl halides but its practical value is limited almost entirely to the bromides.



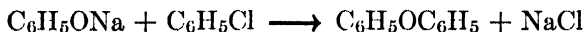
The iodides react readily but are expensive; the chlorides react only under very special conditions and then very slowly. This reaction will be discussed in detail in Chapter XX.

**Phenols and Amines from Aryl Halides.** Commercial methods, involving heat and pressure, have been developed whereby chlorobenzene is converted to phenol or aniline. Phenol is made from sodium

phenoxide, which results when chlorobenzene is heated with sodium hydroxide.



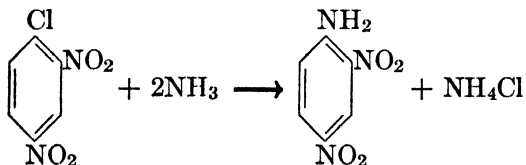
A by-product is phenyl ether.



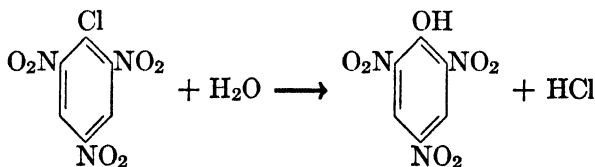
The reaction producing it is suppressed by conducting the process in the presence of phenyl ether.

Aniline is formed when chlorobenzene is heated at about  $200^\circ$  with ammonia (p. 114).

These reactions occur much more readily with aryl halides which carry nitro groups in the *ortho* or *para* positions. For example, 2,4-dinitrochlorobenzene reacts readily with ammonia to give 2,4-dinitroaniline.

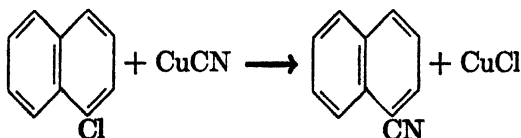


The rapidity of the reaction is due to the activating effect of the nitro group on the halogen atom. That this effect is cumulative is seen in the behavior of picryl chloride, which undergoes hydrolysis with great ease to give picric acid.



This peculiar activating effect, exercised only when the nitro groups are situated *ortho* or *para* to the halogen atom, will be discussed again in connection with the chemistry of aromatic compounds.

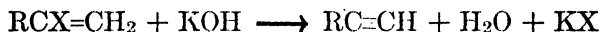
**The Rosenmund-von Braun Nitrile Synthesis.** Aryl halides have been shown in many instances to react with anhydrous cuprous cyanide with or without an added organic base such as pyridine.  $\alpha$ -Chloronaphthalene is converted to  $\alpha$ -naphthonitrile in yields of over 90 per cent.



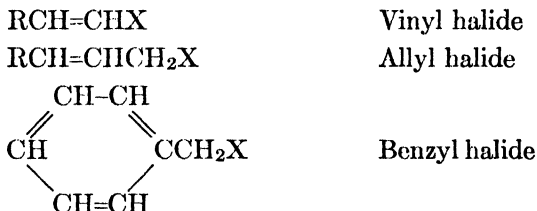
A study of the reaction between aromatic bromides and cuprous cyanide has shown it to be autocatalytic. The reaction time can be shortened by the addition of small amounts of cupric salts and nitriles.

**Vinyl Halides.** Like aryl halides, the vinyl halides are inert to most of the reagents which are used to transform halogen compounds. They form Grignard reagents, however, and these are used occasionally. It is to be noted that this similarity between aryl and vinyl halides may be traced to the fact that both types contain the structural unit,  $\text{>C=C-X}$ .

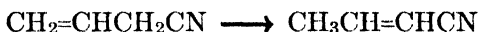
When treated with solid potassium hydroxide or sodium amide, vinyl halides are transformed into acetylenic compounds.



**Allyl Halides.** Allyl halides are distinguished by their unusually high reactivity. This is remarkable when contrasted with the inertness of vinyl halides.



Benzyl halides have the allyl structure and, accordingly, show an enhanced reactivity comparable with that of allyl halides. Allyl cyanide rearranges to crotononitrile in the presence of alkalis.



For this reason cuprous cyanide rather than an alkali cyanide is used to convert allyl halides to the nitriles.

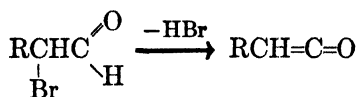


**$\alpha$ -Halogen Carbonyl Compounds.** Halogen atoms which are situated on an  $\alpha$ -carbon atom in a carbonyl compound are very reactive. This reactivity seems to vary as the reactivity of the carbonyl group or as the reactivity which a hydrogen atom would have in the *alpha* position. Thus the  $\alpha$ -halogen atoms show the following order of activity: esters < ketones < aldehydes.

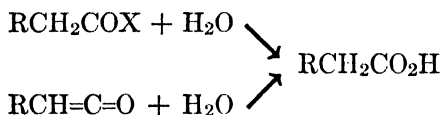
$\alpha$ -Haloaldehydes are not well known and have not been used widely. In many of their reactions they behave as though they had the structure of the isomeric acid halides.



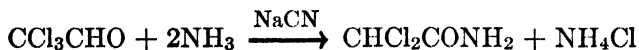
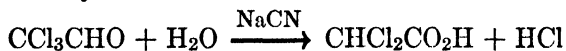
It has been suggested that this peculiar behavior is due to the formation of ketenes by dehydrohalogenation of the aldehydes.



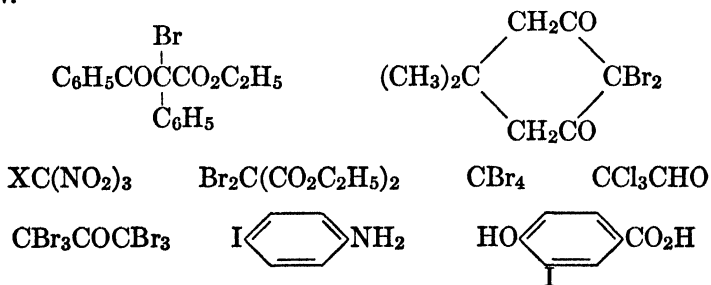
Such a ketene would exhibit many of the reactions of the corresponding acyl halide. For example, both are converted by water into the acid.



Chloral behaves in this manner. In the presence of an alkali cyanide water and ammonia convert it to dichloroacetic acid and dichloroacetamide, respectively.



**Positive Halogen.** Organic halogen compounds are known in which the halogen atom appears to be positive in nature; it tends to separate as  $\text{X}^+$  rather than  $\text{X}^-$  in many reactions. Examples are given below.



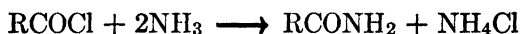
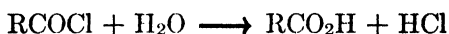
Compounds which contain positive halogen always tend to act as halogenating agents. Such halogen atoms are easily replaced by hydrogen under the influence of reducing agents or alkaline hydrolytic agents.

It is a general rule that if a positive halogen atom is replaced by a hydrogen atom the latter will show a tendency to enolize or to permit hydrogen bond formation. It seems probable that enolization is always conditioned by hydrogen bonding. This assumption would permit the generalization that the factors which confer a positive character upon a

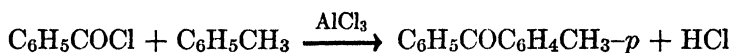
halogen atom likewise give bonding power to the hydrogen atom replacing it.

**$\alpha$ -Halogen ketones** undergo a variety of reactions involving the halogen atom. These are very similar to those listed for alkyl halides. Phenacyl halides ( $\text{C}_6\text{H}_5\text{COCH}_2\text{X}$ ) are unreactive to silver nitrate—an anomaly which may be correlated with the tendency of halogen atoms in such compounds to assume a positive character. The halogen atom in  $\alpha$ -halogen ketones is removed readily by alkaline reagents such as alcoholic potassium hydroxide or aqueous sodium acetate.

**Acyl Halides.** Acyl halides are generally very reactive, the aliphatic members being much more reactive than the aromatic. In general, these substances tend to react to give the corresponding halogen acid and in order to do this will attack any substance having a mobile hydrogen atom. Water, alcohols, ammonia, and primary and secondary amines are a few of these.



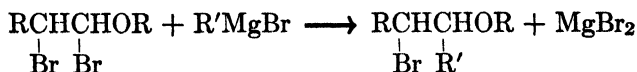
Acyl halides are widely employed in the Friedel-Crafts synthesis of ketones (p. 96). For example, benzoyl chloride reacts with toluene in the presence of aluminum chloride to give phenyl *p*-tolyl ketone.



**$\alpha$ -Halogen Ethers.** The action of Grignard reagents on  $\alpha$ -halogen ethers furnishes a general method for preparing mixed ethers.



Treatment of an  $\alpha,\beta$ -dibromo ether with a Grignard reagent replaces only the *alpha* bromine atom.



**Halohydrins.** These substances are hydroxy halides and react in much the same way as alkyl halides. The products are alcohols, however, and may undergo subsequent transformations.

**Polyhalogen Compounds.** Accumulation of halogen atoms on the same carbon atom tends to diminish their reactivity. This is exemplified by the stability of chloroform and carbon tetrachloride, neither of which will give a precipitate with silver nitrate.

Exceptional in this respect are benzyl chloride, benzal chloride, and benzotrichloride—a series in which the ease of hydrolysis increases with

the increase in chlorine content. This recalls the exceptional behavior of allyl halides—a group with which benzyl halides may be classified. Also, as was mentioned in connection with the action of phosphorus pentahalides on methyl aryl ketones, homologs of aryl halides of the type  $\text{ArCX}_2\text{CH}_2\text{R}$  readily lose one molecule of hydrogen halide to yield vinyl halides,  $\text{ArCX}=\text{CHR}$ .

Chloroform reacts with primary amines in the presence of alkalis to give isonitriles or carbylamines—a reaction which serves as a test for the presence of primary amines.

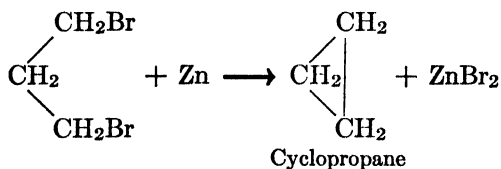


The odor of an isonitrile is so peculiar and so strong that its presence cannot be overlooked.

An important general reaction of 1,2-dihalogen compounds is their conversion to olefinic derivatives by the action of zinc.



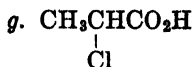
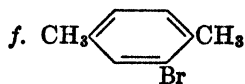
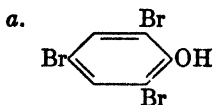
A somewhat similar reaction may take place when 1,3-dihalogen compounds react with zinc. For example, 1,3-dibromopropane reacts with zinc to give cyclopropane, now used as a general anesthetic.

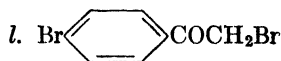
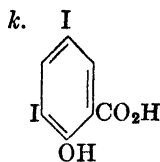
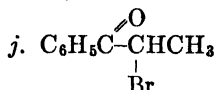
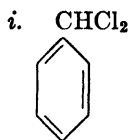
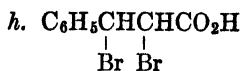


This is an intramolecular Wurtz reaction discovered by Freund. Other cyclanes can be made by this method, but it is of practical value only for this one.

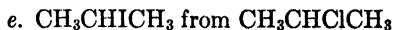
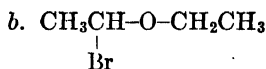
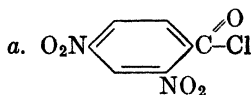
### PROBLEMS

1. Indicate for each of the following compounds a convenient method of synthesis. The organic compounds used as starting materials are to be halogen-free. For each method state the reagents used and indicate the conditions, catalysts, etc., which favor the reaction.

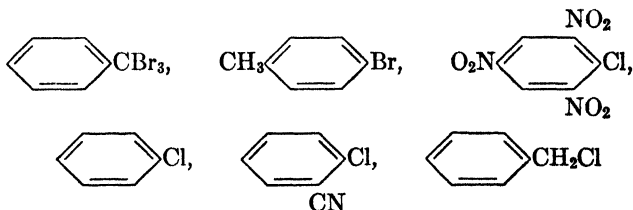




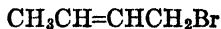
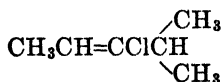
2. Synthesize the following compounds from organic compounds containing no halogen, giving conditions, reagents, and catalysts.



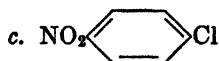
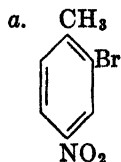
3 a. Arrange the following compounds in the order of their reactivity toward alcoholic silver nitrate.



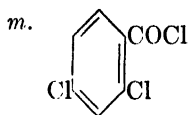
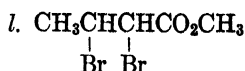
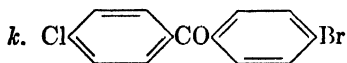
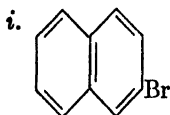
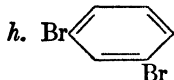
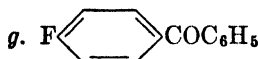
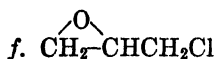
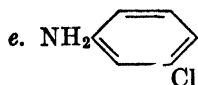
b. Arrange the following compounds in the order of their reactivity toward water and aqueous alkali.



4. For each of the following compounds give a useful method of synthesis involving the introduction of halogen into the molecule. Indicate the reagents and special conditions used.

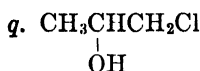
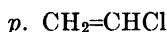






n. fumaryl chloride

o. phthalyl chloride



### SUGGESTED READINGS

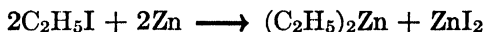
- VAUGHAN and RUST, "The High Temperature Chlorination of Paraffin Hydrocarbons," *J. Org. Chem.*, **5**, 449 (1940).
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## CHAPTER XX

### ORGANOMETALLIC COMPOUNDS

#### HISTORICAL

The term organometallic is used to denote those substances in which a metal is joined directly to carbon. The first of these to be made was diethylzinc, prepared by Frankland in 1849 from ethyl iodide and the metal.



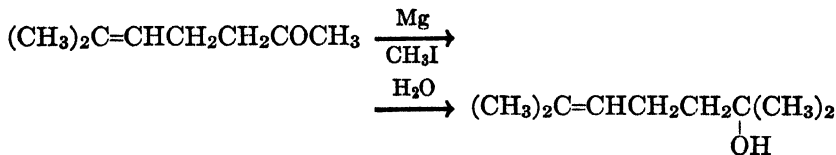
The alkylzinc compounds, although inflammable and difficult to handle, proved invaluable. They were volatile and their molecular weights could be determined. This was of great assistance in assigning the proper valence to the metal. Moreover, these compounds were useful in synthesis, serving many of the purposes for which we now use the Grignard reagent.

As time went on, organometallic derivatives containing other metals were synthesized. Among these are compounds of magnesium, lithium, mercury, lead, and aluminum. Nearly all the metals are capable of forming such derivatives.

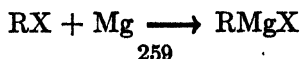
It will be convenient to discuss the magnesium compounds first since they have been carefully studied and illustrate most of the types of reactions found in the entire group of organometallic compounds.

#### THE GRIGNARD REAGENT

✓ The Grignard reaction was first effected by Barbier in 1899. By treating a methylheptenone with methyl iodide and magnesium he prepared the corresponding dimethylheptenol.



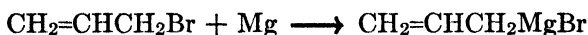
In 1900 Grignard divided the synthesis into two steps, the first of which is that known by his name.



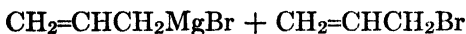
**Preparation.** Grignard reagents are nearly always prepared by the interaction of the halogen compound and magnesium in ethyl ether. Other ethers or tertiary amines are used also, and in some instances the solvent is dispensed with. Nearly all organic halogen compounds give Grignard reagents, exclusive, of course, of those which contain functional groups which are attacked by the reagent.

As has been indicated, alkyl and aryl chlorides, bromides, and iodides form  $\text{RMgX}$  derivatives. Aryl chlorides react only under special conditions.

Allylmagnesium bromide can be made only by slow addition of a solution of the halide to finely divided magnesium.

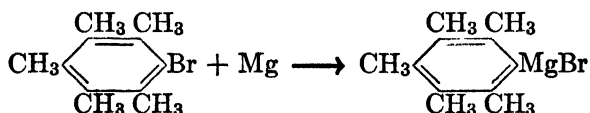


This serves to suppress the coupling reaction.



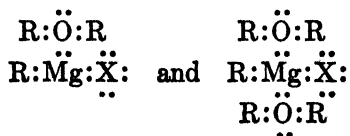
In order to initiate reaction between the halide and magnesium it is a general practice to add a crystal of iodine to the mixture. Magnesium iodide, hydrogen iodide, and methylmagnesium iodide have been used for the same purpose. Sometimes the metal is activated by preliminary heating with iodine or by treatment with an alkyl halide. The only theory yet put forward which explains the action of these catalysts is that which postulates a magnesian halide as the true catalyst.

Success in difficult cases has been achieved by the "entrainment" method. Bromopentamethylbenzene, for example, is mixed with ethyl bromide and the mixture allowed to react with magnesium.



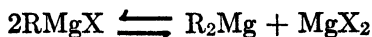
The reaction between ethyl bromide and the metal serves to induce the aryl bromide to react.

**Structure.** The role played by ethers in the preparation and use of the Grignard reagent is probably to form coordination compounds with the  $\text{RMgX}$  molecule.



Actually, there is evidence that  $\text{RMgX}$  forms both a mono- and a di-etherate. These probably have the constitution indicated above. This type of combination is possible for electron donors which do not react otherwise with the reagent. Pyridine (p. 455) is an example, and it has been used in place of an ether as solvent.

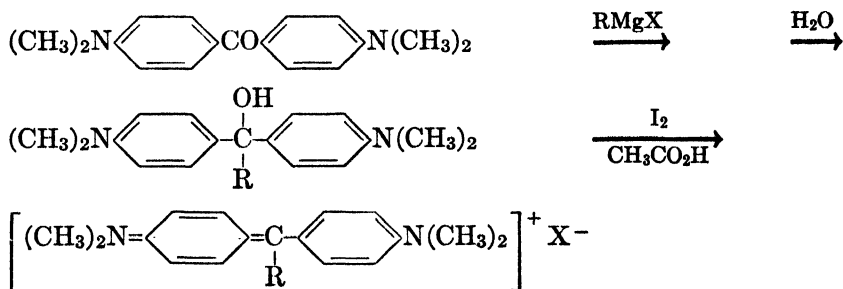
Of great interest is the fact that solutions of Grignard reagents conduct an electric current, and because of this it is generally believed that the reagent tends to dissociate into the ions  $\text{R}^-$ ,  $\text{Mg}^{++}$ ,  $\text{X}^-$ ,  $\text{RMg}^+$ , and  $\text{MgX}^+$ . It is believed that the following equilibrium also exists in solutions of the reagent.



Evidence for this is the fact that addition of dioxane (p. 60) causes all the halogen to be precipitated as  $\text{MgX}_2$  and  $\text{RMgX}$ . The halogen-free solution still has the characteristic properties of an organometallic derivative. These must be due to the presence of  $\text{R}_2\text{Mg}$ .

So far all the reactions of the Grignard reagent can be explained satisfactorily by use of the simple formula  $\text{RMgX}$ .

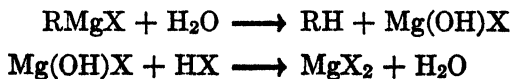
**Analysis.** A qualitative test for the Grignard reagent consists in mixing the solution with Michler's ketone in benzene, adding water and finally iodine.



If  $\text{RMgX}$  is present a green-blue color is observed.

Methylmagnesium halides react with water to give methane, and advantage is taken of this to determine the amount of reagent present. All that is necessary is to collect the gas and measure its volume. This method is applicable to a few other Grignard reagents—those which yield gaseous hydrocarbons.

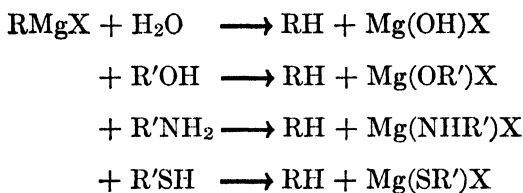
A general method of quantitative estimation consists in decomposing the reagent with water and titrating the basic magnesium salt with standard acid.



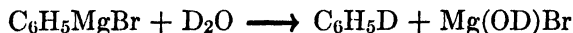
### Reactions of the Grignard Reagent

The reactions of the Grignard reagent are very numerous and lead to a wide variety of products. The types of reactions are, however, few in number. It will be helpful to consider each type separately.

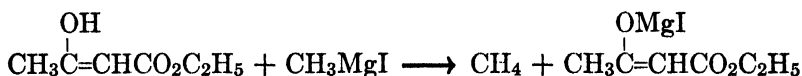
**1. Compounds Containing Active Hydrogen Atoms.** Water, alcohols, primary and secondary amines, many amides, and sulphydryl compounds decompose the Grignard reagent.



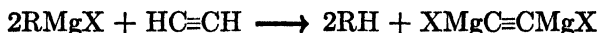
The decomposition of a Grignard reagent with heavy water produces a deuterium compound; phenylmagnesium bromide yields monodeutero-benzene.



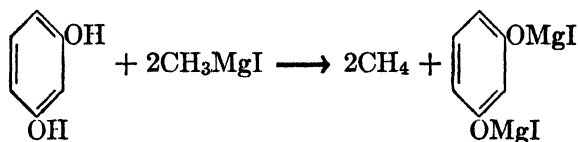
In general, a hydrogen atom attached to any element other than carbon will react in this manner. Such hydrogen atoms are said to be *active*. Many carbonyl compounds give this reaction also because they react in the enol modification, e.g., ethyl acetoacetate reacts with methylmagnesium iodide to give 1 mole of methane.



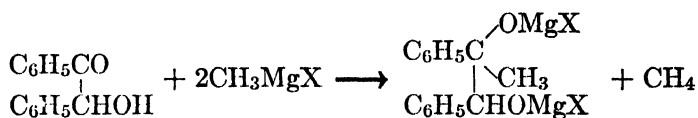
There are some instances in which hydrogen on carbon is sufficiently reactive to decompose the reagent. Acetylene is an example.



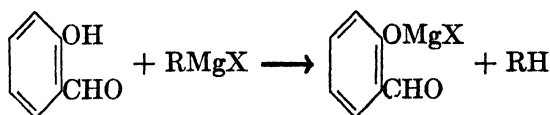
The reaction of active hydrogen compounds with  $\text{RMgX}$  compounds is occasionally employed to make hydrocarbons. Its common use, however, is in analytical work. It forms the basis of the Tschugaeff-Zerevitinoff method of determining active hydrogen atoms. This method consists in treating a weighed amount of the compound to be tested with an excess of a methylmagnesium halide and measuring the methane evolved. One mole of resorcinol, for example, gives 2 moles of methane.



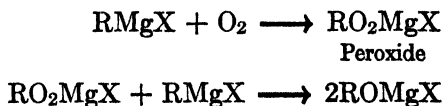
A modification of this method is due to Kohler. He devised a means of preparing and storing a *standard solution* of methylmagnesium iodide. An excess of the reagent is used and after the reaction is complete the unused reagent is determined by addition of water and measuring the methane evolved. If 1 mole of benzoin is treated with 3 moles of reagent it will be found that 1 mole of methane is evolved at once and that a total of 2 moles of reagent is used. This leads to the conclusion that the molecule contains a carbonyl group in addition to one active hydrogen atom.



It is most important to avoid this type of reaction in synthetic work. Thus the ether and reactants should be free from water, alcohols, and all other compounds which have active hydrogen atoms. It is to be emphasized that this type of reaction is faster than those generally sought in synthetic work. When salicylaldehyde, for instance, is treated with a Grignard reagent the hydroxyl group decomposes the reagent before the aldehyde group is attacked.



2. **Oxygen, Sulfur, and Halogens.** Chemiluminescence is observed when a Grignard reagent is exposed to air or oxygen;  $\text{BrMgC}_6\text{H}_4\text{MgBr}$  gives a particularly intense glow. The reaction is a complex one and seems to consist of the following steps.



From the alcoholate so formed the alcohol is obtained by treatment with dilute acids.



The absorption of oxygen is very rapid, and care must be taken to exclude it from the apparatus containing the reagent. This is generally done by using a volatile ether as solvent. Ethyl ether vapors, for example, flow out of the apparatus so rapidly as to prevent the oxygen from entering.

Aliphatic reagents lead to high yields of the corresponding alcohols but this has little or no synthetic value since the halides used in preparing reagents in the first place are generally made from the alcohols.

In the aromatic series where the reaction might be useful it is much more complex. Only unsatisfactory yields of phenols can be gotten in this way.

Sulfur reacts similarly, giving rise to mercaptans and thiophenols. Rubber stoppers normally contain uncombined sulfur and if the reagent is allowed to come into contact with them the product will be contaminated with unpleasant-smelling sulfur derivatives.

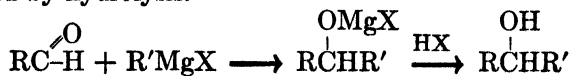
Halogens cleave  $\text{RMgX}$  compounds as follows:



This reaction gives excellent yields of iodo compounds and provides a method for getting these from the corresponding chloro or bromo compounds. Propyl bromide, isoamyl chloride, bromobenzene, and *p*-bromotoluene give the corresponding iodo derivatives in yields of 80 per cent.

**3. Addition Reactions.** Compounds containing double or triple bonds generally react additively with the reagent. The common types of linkages are  $\text{C}=\text{O}$ ,  $\text{C}=\text{S}$ ,  $\text{C}=\text{N}$ ,  $\text{C}\equiv\text{N}$ ,  $\text{N}=\text{O}$ , and  $\text{N}=\text{N}$ . Ethylenic and acetylenic linkages do not react in this manner. This is not surprising, for one would not expect a magnesium atom to show any great tendency to leave one carbon atom for another.

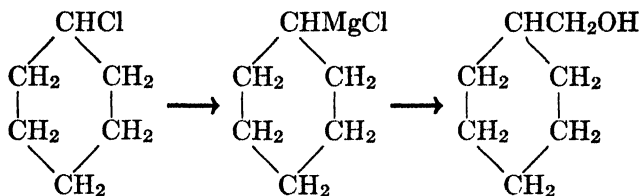
Aldehydes, the most reactive of the carbonyl compounds, combine readily with  $\text{RMgX}$  to give alcoholates from which secondary alcohols are obtained by hydrolysis.



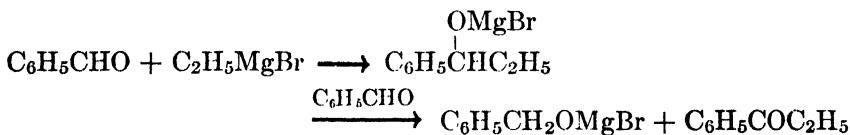
Formaldehyde, as already noted (p. 71), leads to the formation of primary alcohols.



The reaction is useful in building up a carbon chain (p. 85), e.g., octyl and undecyl alcohols are made from their next lower homologs in this way. Cyclohexylcarbinol is obtained from cyclohexyl chloride in 65 to 70 per cent yields by this method.

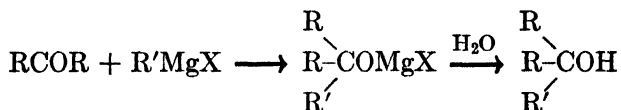


If excess aldehyde is present the carbinolates may undergo oxidation. Under these conditions, for example, benzaldehyde and ethylmagnesium bromide give propiophenone.

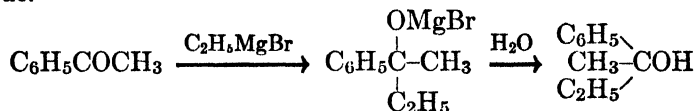


The halomagnesium alcoholates also catalyze condensation reactions of the aldol type. In most cases, therefore, an excess of Grignard reagent must be present if good yields are to be obtained. This is accomplished by using an excess of this reagent and adding the other reactant to it gradually.

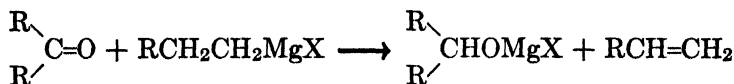
Ketones are converted to tertiary alcohols by the Grignard method (p. 78).



In practice this method of making tertiary alcohols is limited to those in which the three radicals are different. An example is the synthesis of ethylmethylphenylcarbinol from acetophenone and ethylmagnesium bromide.

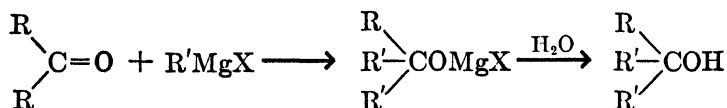
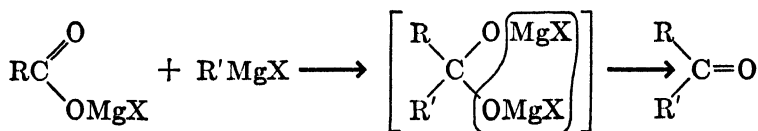
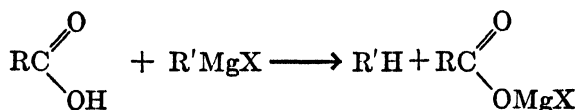


Ketones which have large and complex radicals often react very slowly, and reduction is then frequently observed.



Acids contain one active hydrogen atom and react with  $\text{RMgX}$  to give 1 mole of hydrocarbon. The salt will react with any excess reagent; in this way carbinols form.

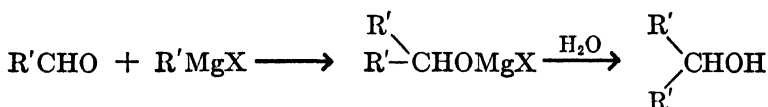
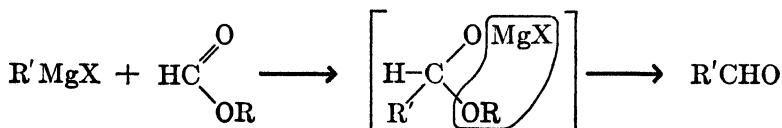




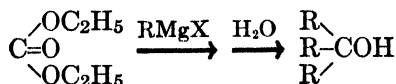
This method is not used because it is wasteful of the reagent.

Esters, as indicated earlier (p. 94), generally lead to the formation of tertiary alcohols.

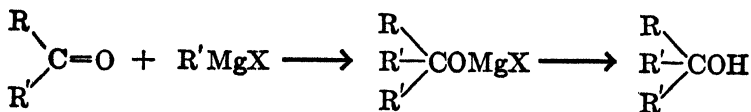
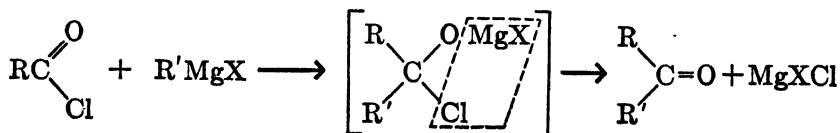
Formates give secondary alcohols.



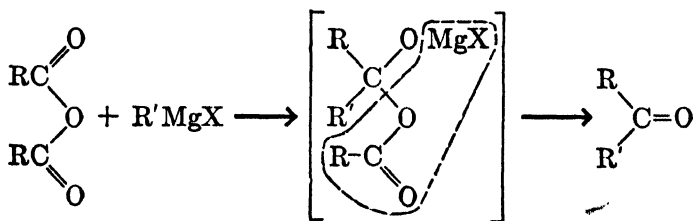
Ethyl carbonate is used to prepare tertiary alcohols in which all three radicals are alike.



Acid chlorides react very rapidly with Grignard reagents. Advantage may be taken of this in the synthesis of ketones.

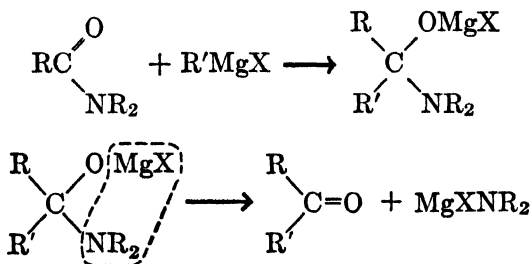


The rate of the first reaction is faster than that of the second, and if the process is properly conducted the ketone can be isolated. Similar results are obtained with acid anhydrides.

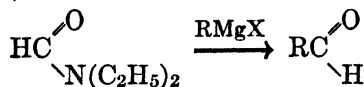


The use of an excess of reagent converts both acid chlorides and anhydrides to the corresponding tertiary alcohols.

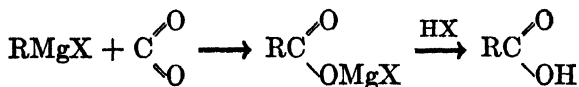
Amides of the types  $\text{RC}(=\text{O})\text{NH}_2$  and  $\text{RC}(=\text{O})\text{NHR}$  have active hydrogen and decompose the reagent. Useful synthetic methods have, however, been developed, employing amides of the type  $\text{RC}(=\text{O})\text{NR}_2$ . The reagent reacts with them to give a fairly stable intermediate which can be isolated and decomposed; ketones are formed.



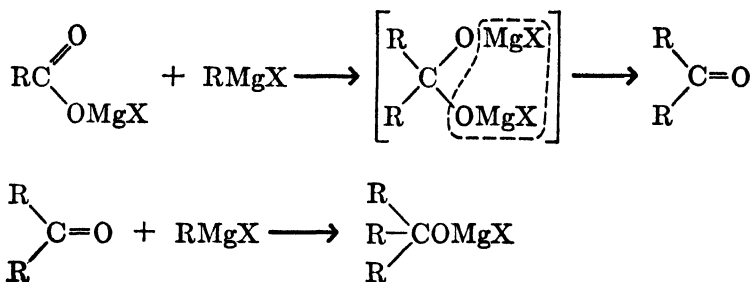
Formamides of this type lead to the production of aldehydes (Bouveault's method).



Carbon dioxide is useful in the synthesis of acids from the Grignard reagent.



This reaction is run at low temperatures to prevent transformation of the salt into the carbinol.

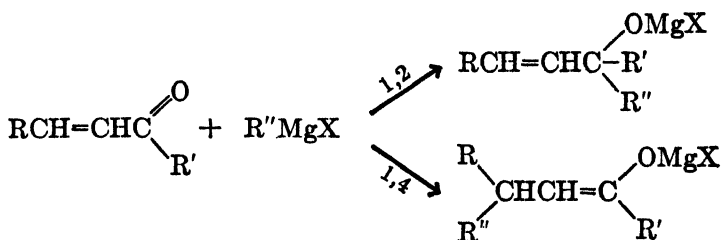


Dry-ice can be used advantageously since it not only furnishes the carbon dioxide but acts as a refrigerant as well. Moreover, the reagent can be poured on the dry-ice, thus obtaining a more favorable concentration of the reactants. The synthesis finds use in the preparation of acids from secondary and tertiary halides, which do not react smoothly with alkali cyanide to give nitriles. An example has already been given (p. 55).

TABLE XXVII  
1,2 AND 1,4 ADDITION

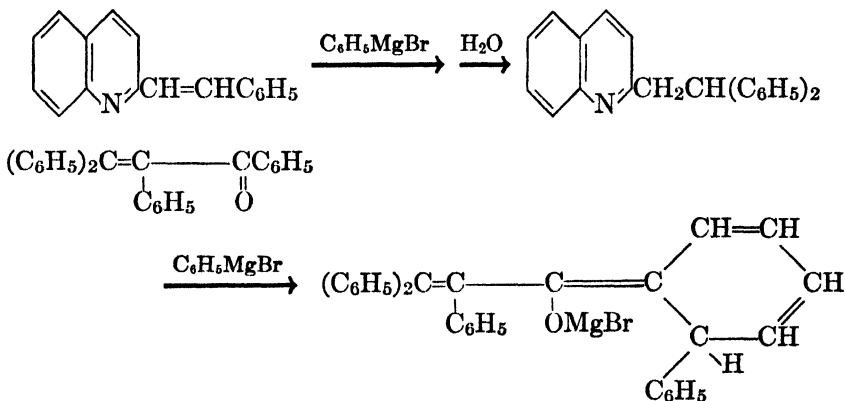
	Per Cent of 1,4 Addition	
	$\text{C}_2\text{H}_5\text{MgBr}$	$\text{C}_6\text{H}_5\text{MgBr}$
$\text{CH}_2=\text{CHCHO}$	0	0
$\text{CH}_3\text{CH}=\text{CHCOCH}_3$	75	40
$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C}=\text{CHCOCH}_3 \\ \diagup \\ \text{CH}_3 \end{array}$	0	0
$\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}_3$	60	12
$\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}_2\text{CH}_3$	71	40
$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C}_6\text{H}_5\text{CH}=\text{CHCOCH} \\ \diagup \\ \text{CH}_3 \end{array}$	100	88
$\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}(\text{CH}_3)_3$	100	100
$\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}_6\text{H}_5$	99	94
$\text{C}_6\text{H}_5\text{C}\equiv\text{CCOC}_6\text{H}_5$	...	0

Ketones and esters containing a conjugated system of the type  $\text{C}=\text{C}-\text{C}=\text{O}$  may react with the Grignard reagent either in the 1,2 or the 1,4 manner.



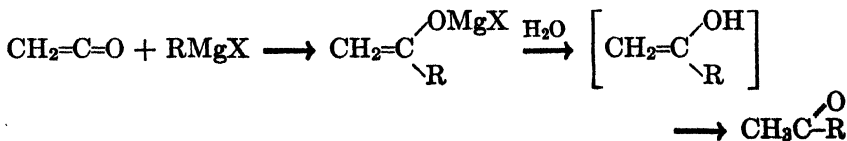
The mode of the addition depends on the nature of R, R', and R''. If R is large 1,2 addition is favored. If R' is large 1,4 addition is favored. Aliphatic reagents (R'' equals alkyl) favor 1,4 addition whereas aromatic reagents (R'' equals aryl) favor 1,2 addition. Frequently both 1,2 and 1,4 addition occur simultaneously. The examples given in Table XXVII illustrate these generalizations.

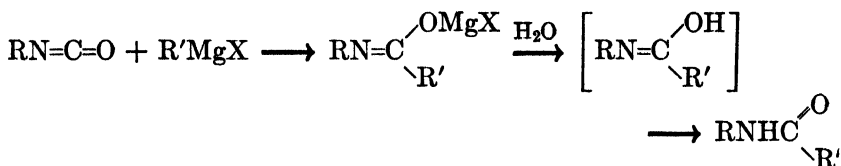
1,4 Addition is also known to occur in lateral-nuclear systems such as are found in benzalquinaldine and  $\alpha,\beta$ -diphenylbenzalacetophenone.



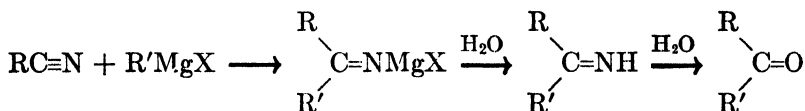
In the latter instance the reaction does not take place under ordinary conditions; to bring it about most of the ether is replaced by benzene and the higher-boiling solution is allowed to reflux. This is called "forcing."

Among the most reactive carbonyl compounds are the ketenes and the isocyanates. They react rapidly with the Grignard reagent and yield, respectively, ketones and amides.



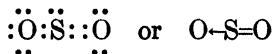


The Grignard reagent reacts with nitriles to give imine derivatives from which ketones are formed by hydrolysis.

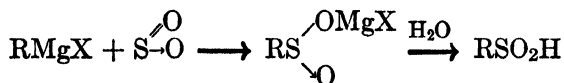


The method is applicable to aliphatic nitriles in which R is primary and larger than methyl. Aromatic nitriles that have no *ortho* substituents also undergo the reaction. Satisfactory yields are obtained only when 4 moles of reagent are used for 1 mole of nitrile.

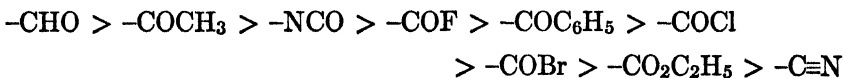
The electronic formula of sulfur dioxide indicates that one oxygen atom is linked to the sulfur atom by a double bond.



The addition reaction with the Grignard reagent is that which would be predicted on the basis of this formula. The products are sulfinic acids.



The use of the Grignard reagent with polyfunctional molecules brings up the question of relative reactivities of the groups. Enteman and Johnson, using phenylmagnesium bromide, have established the following order:

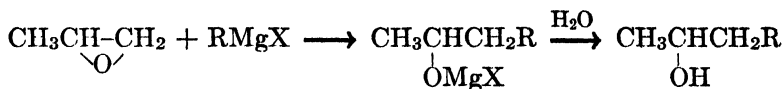


The fact that  $-\text{COF}$  stands ahead of  $-\text{COCl}$  appears to show that the reaction is additive and not metathetical.

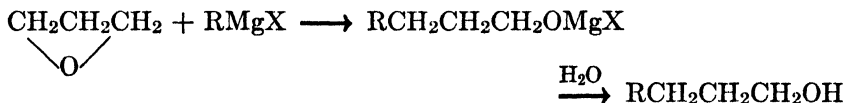
✓ **4. Cyclic Ethers.** Ethers in general are unaffected by the Grignard reagent, but three- and four-membered cyclic ethers undergo reaction with accompanying opening of the ring. Ethylene oxide is used to lengthen the carbon chain.



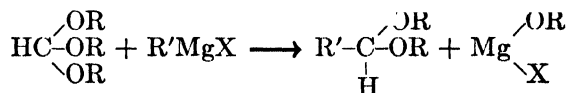
Propylene oxide reacts similarly but yields secondary alcohols.



Although trimethylene oxide reacts to form primary alcohols, it has not found general application in the lengthening of carbon chains; the yields are not high and the oxide has been a relatively rare reagent.

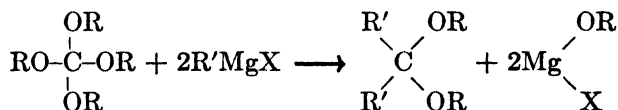


**5. Ortho Esters.** Orthoformic esters react with Grignard reagents to give acetals of aldehydes.



This has been used in the preparation of aldehydes.

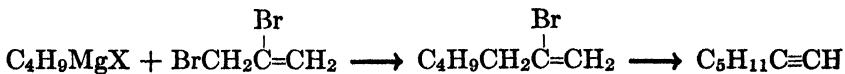
Orthocarbonic esters, similarly, lead to acetals of ketones.



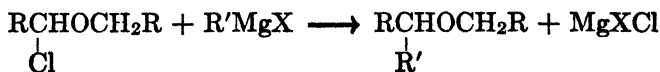
**6. Alkylation by Means of the Grignard Reagent.** Compounds such as allyl bromide and benzyl chloride which contain very reactive halogen atoms are frequently alkylated by interaction with  $\text{RMgX}$ .



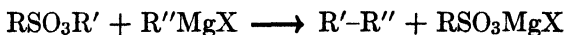
The important method of Lespieau and Bourguel is based on this reaction. Bromoallyl bromide reacts with butylmagnesium bromide, for example, to give a bromoheptene which is converted to 1-heptyne by the action of alkali.



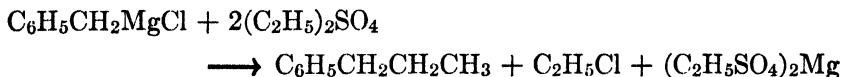
$\alpha$ -Halogen ethers are alkylated readily.



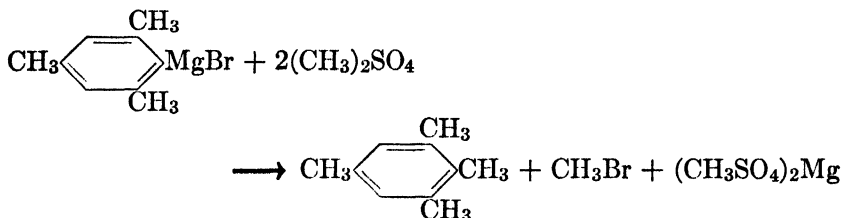
Esters of sulfonic acids resemble alkyl halides in this respect.



Alkyl sulfates behave similarly. *n*-Propylbenzene is made in yields of 70 to 75 per cent by the interaction of benzylmagnesium chloride and ethyl sulfate.

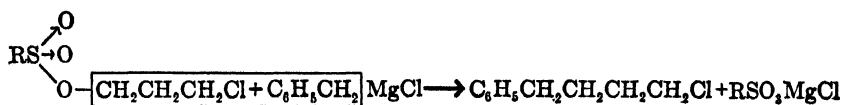


Similarly, isodurene is formed by treating mesitylmagnesium bromide with methyl sulfate.

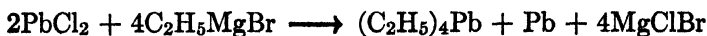


The similarity of alkyl sulfates and alkyl halides is readily understood if it is recalled that both are in reality esters which, however, have no multiple linkages which the Grignard reagent may attack.

A useful application of this method is found in alkylation by means of  $\gamma$ -chloropropyl sulfonates.



Many inorganic halides are alkylated by treatment with  $\text{RMgX}$ .



✓  
**7. Coupling of the Grignard Reagent.** Compounds containing very reactive halogen atoms tend to couple the alkyl groups of the reagent. Thus cupric chloride converts benzylmagnesium chloride largely to bibenzyl.



Silver bromide is particularly effective; by its use high yields have been obtained of coupling products such as biphenyl, bianisyl, *n*-octane, and bicyclohexyl. Other metal salts also have been used. In all cases the salt acts as an oxidizing agent.

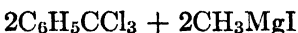
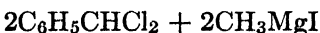
Organic halides may also bring about coupling. For example, benzyl chloride reacts with methylmagnesium iodide to give about 75 per cent yields of bibenzyl.



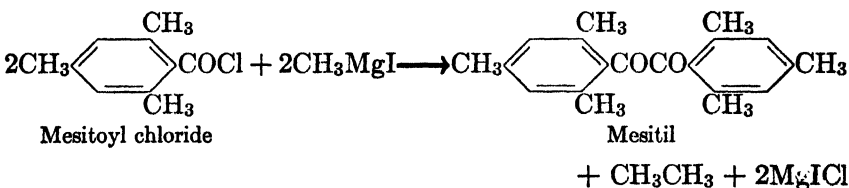
A certain amount of alkylation is also observed.



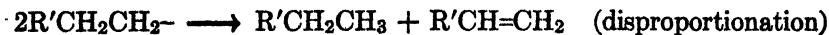
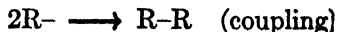
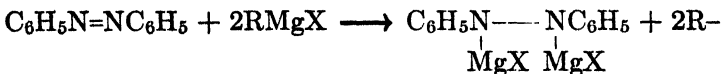
Most of the coupling reactions of the latter type involve benzyl halides or their derivatives. Benzal chloride and benzotrichloride are interesting examples. With methylmagnesium iodide they yield, respectively, stilbene chloride and tolane tetrachloride.



It is remarkable that hindered benzoyl chlorides undergo this type of coupling also. From mesitoyl chloride and methylmagnesium iodide mesitol is obtained.

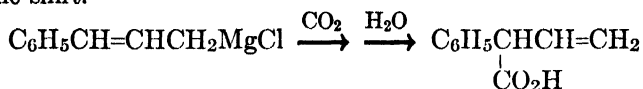


Azo compounds react with the Grignard reagent in a peculiar manner. Each nitrogen atom takes up  $\text{MgX}$  and the alkyl groups couple or undergo disproportionation.

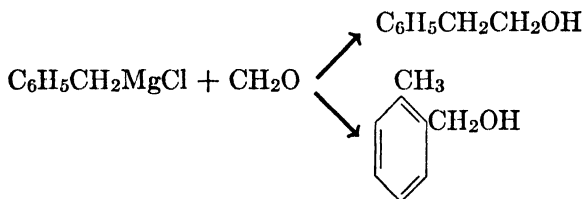




**8. Rearrangements.** Halides of the allyl type form Grignard reagents which frequently give abnormal products. With carbon dioxide, cinnamylmagnesium chloride gives chiefly the acid which would result from an allylic shift.



Similarly, benzylmagnesium chloride reacts with formaldehyde to give not only  $\beta$ -phenylethyl alcohol but also *o*-tolylcarbinol.



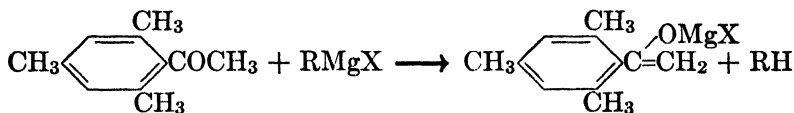
**9. Other Reactions of the Grignard Reagent.** Ketones and esters whose carbonyl groups are relatively unreactive toward the reagent often give rise to reactions other than addition. Three types of these so-called abnormal reactions have been observed: reduction, enolization, and condensation. Which of the four reactions will take place depends largely on the nature of the radicals adjoining the carbonyl group and in the Grignard reagent.

TABLE XXVIII  
REACTIONS OF THE GRIGNARD REAGENT

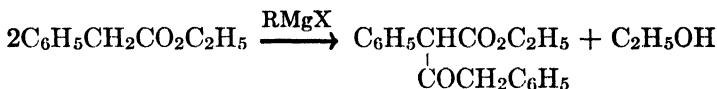
	$\text{CH}_3\text{MgI}$	$n\text{-C}_3\text{H}_7\text{MgBr}$	$(\text{CH}_3)_2\text{CHMgBr}$	$(\text{CH}_3)_3\text{CMgCl}$
$\text{CH}_3\text{CHO}$	AA		A	AA
$\begin{array}{c} \text{CH}_3 \backslash \\ \text{CHCHO} \\ \text{CH}_3 / \end{array}$	A		AA	AR
$(\text{CH}_3)_3\text{CCHO}$		AA	AR	RR
$\text{CH}_3\text{COC}(\text{CH}_3)_3$	AA		EC	EC
$(\text{CH}_3)_2\text{CHCOCH}(\text{CH}_3)_2$	AA		RR	RR
$\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$			EECC	
$(\text{CH}_3)_3\text{CCO}_2\text{C}_2\text{H}_5$				no reaction

When primary alkyl groups are present the addition or normal reaction always predominates. Complications arise, however, when branched radicals are involved. Table XXVIII shows some of these

effects. A, R, E, and C denote, respectively, addition, reduction, enolization, and condensation; if the yield is 50 per cent or better the letter is doubled. An equation illustrating reduction has been given earlier (p. 265). The enolization is well illustrated by the behavior of acetomesitylene; the product is the enolate.



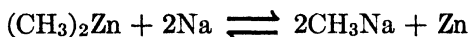
The condensations observed are of the acetoacetic ester type.



It has not been possible to use Grignard reagents to prepare alcohols containing more than two secondary or tertiary alkyl groups.

### Other Organometallic Compounds

✓ All the alkali metals form organometallic compounds. These are usually made by the action of the metal on the  $\text{R}_2\text{Hg}$  or  $\text{R}_2\text{Zn}$  compound.



✓ They react in much the same way as do Grignard reagents. Carbon dioxide, for example, converts them to the sodium salts of acids.



✓ They are intermediates in the Wurtz-Fittig reaction, which is useful for the formation of  $\text{ArR}$  compounds.



The use of arylsodiums is often convenient. In preparing triphenylcarbinol from ethyl benzoate and chlorobenzene, magnesium is nearly useless whereas sodium gives a very good yield. Presumably phenylsodium is the reagent involved in this condensation.

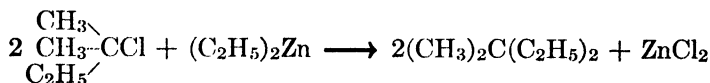
The lithium compounds may be prepared by the action of the metal on  $\text{RX}$ .



Aryl- and alkylolithiums can be prepared in the same manner as  $\text{RMgX}$  compounds and are sometimes more useful. As an example, benzalacetophenone reacts with phenyllithium chiefly in the 1,2 manner.

Organozinc compounds are less reactive than the corresponding magnesium compounds. This is well illustrated by the fact that dialkylzincs can be handled in an atmosphere of carbon dioxide. The zinc derivatives generally have been superseded in synthetic work by magnesium compounds. However, they appear to offer definite advantages in some types of preparations.

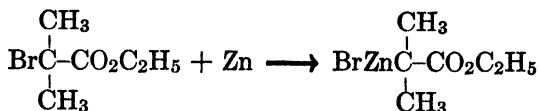
The synthesis of hydrocarbons of the type  $\text{R}_4\text{C}$  can be accomplished in yields of 25 to 50 per cent by treating a tertiary alkyl halide with a dialkylzinc. An example is dimethyldiethylmethane.



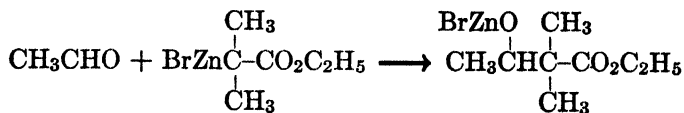
The Blaise method for making ketones consists in the interaction of an acid chloride and an alkylzinc iodide.



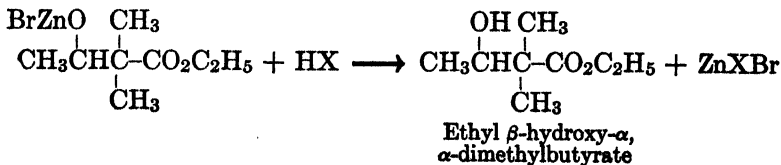
**The Reformatsky Reaction.** Closely allied to certain of the Grignard condensations is the Reformatsky reaction. It involves the condensation of an  $\alpha$ -halo ester with an aldehyde or ketone by use of metallic zinc. An example is the formation of ethyl  $\beta$ -hydroxy- $\alpha,\alpha$ -dimethylbutyrate from acetaldehyde and ethyl  $\alpha$ -bromoisobutyrate. The reaction creates a new carbon-to-carbon linkage and appears to take place in three steps. An organozinc halide is formulated as the initial product.



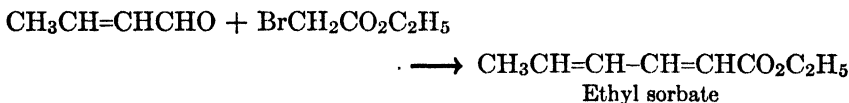
Addition of this compound to the carbonyl group of the aldehyde occurs next.



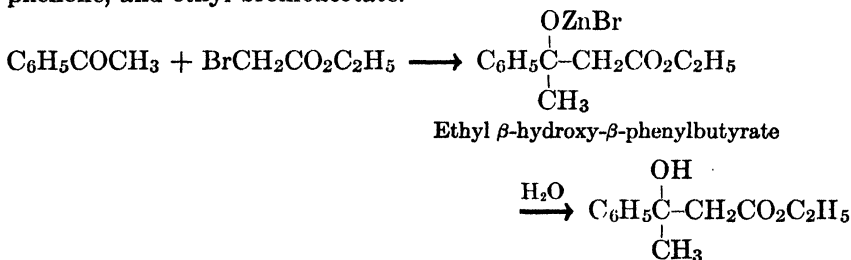
The final step involves decomposition with dilute acid.



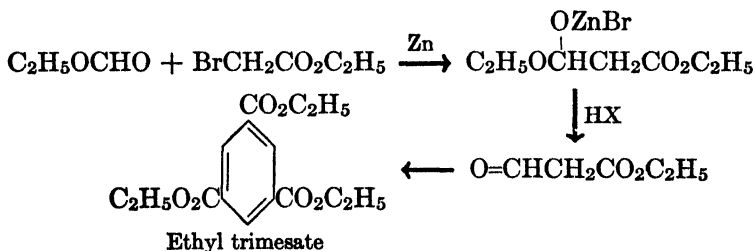
Frequently the hydroxy ester is not isolated. Instead, the product is the corresponding unsaturated ester formed, presumably, by dehydration of the hydroxy ester. An illustration is the formation of ethyl sorbate from zinc, crotonaldehyde, and ethyl bromoacetate.



Application of the Reformatsky method to ketones is illustrated by the preparation of ethyl  $\beta$ -hydroxy- $\beta$ -phenylbutyrate from zinc, acetophenone, and ethyl bromoacetate.



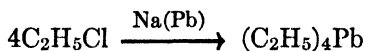
The use of zinc instead of magnesium in the Reformatsky method has the advantage that the organozinc intermediate has little tendency to attack ordinary esters. It is this fact which makes the method possible; otherwise, the organozinc compound would be unstable since it contains groups which would interact. It is true that a few esters can be used instead of aldehydes or ketones but these are formates, oxalates, or  $\alpha$ -alkoxy esters—compounds in which the ester carbonyl group possesses unusually high activity. An extremely interesting example is the condensation of ethyl bromoacetate with ethyl formate.



The expected aldehyde ester is not obtained. Under the conditions of the experiment it trimerizes to give ethyl trimesate.

Organocadmium compounds are still less reactive than are organozinc compounds and have proved to be more useful than the zinc compounds for transforming acid chlorides into ketones.

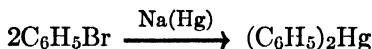
✓ The most important technical use of organometallic compounds is that of tetraethyllead as an antiknock compound. It is made from ethyl chloride and sodium-lead alloy (p. 55).



✓ Organomercury compounds have been made in numerous ways. A Grignard reagent acts on mercury bichloride to give the corresponding dialkylmercury.



✓ Diphenylmercury is made by treating bromobenzene with sodium amalgam.



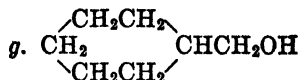
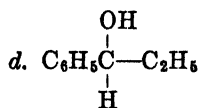
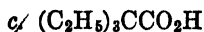
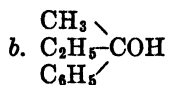
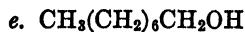
✓ Many aromatic compounds may be mercurated by treatment with mercury salts (p. 430).

### PROBLEMS

1. Outline useful synthetic methods for obtaining the following substances from readily available materials:

- a. *p*-Iodotoluene
- b. *p*-Chlorobenzophenone
- c. Ethylmethylphenylacetic acid
- d. 1-Heptyne
- e. *n*-Propylbenzene
- f. Triphenylstibine
- g. 1,1-Diphenylethylene
- h.  $\alpha$ -Naphthoic acid
- i.  $\alpha$ -Bromocaproic acid
- j. 1-Bromo-2-phenylethane

2. For each of the following compounds indicate a method of synthesis which involves a Grignard reagent:



3. Write an equation for the reactions between methylmagnesium iodide and (a) aniline, (b) oxygen, (c) benzoic acid.
4. A sample of 0.098 g. of a compound whose formula is  $C_{10}H_{12}O_4$  reacts with methylmagnesium iodide to give 22.3 cc. of methane under standard conditions. How many of the oxygen atoms are present as hydroxyl groups?

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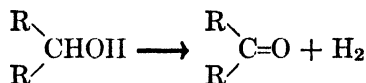
## CHAPTER XXI

### THE SYNTHESIS OF CARBONYL COMPOUNDS

The synthesis of esters usually involves esterification of the corresponding acids and presents no serious problem. Aldehydes and ketones, on the other hand, are often very difficult to make and a large number of procedures have been developed for their preparation. The more important types of these synthetic methods will be discussed.

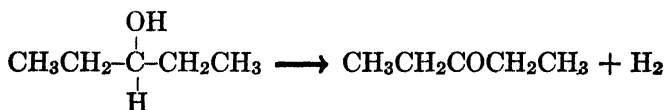
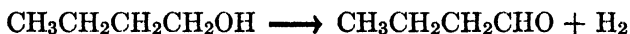
#### Oxidation of Alcohols

The dehydrogenation of primary and secondary alcohols leads to aldehydes (p. 53) and ketones (p. 53), respectively.



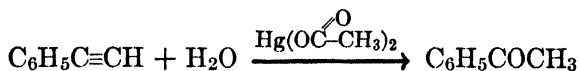
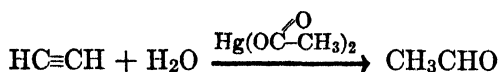
This method is of especial value in the aliphatic series where primary and secondary alcohols are readily available.

In the laboratory a mixture of potassium dichromate and sulfuric acid is the usual oxidizing agent. Industrial practice generally involves catalytic dehydrogenation over a metal at about 300°. *n*-Butyraldehyde and diethyl ketone are examples of compounds which are manufactured in this way. The catalyst may be platinum, copper, or silver.



#### Hydration of Acetylenic Compounds

Acetylenic compounds take up the elements of water in the presence of mercuric salts. For instance, acetylene and phenylacetylene yield respectively, acetaldehyde (p. 23) and acetophenone.



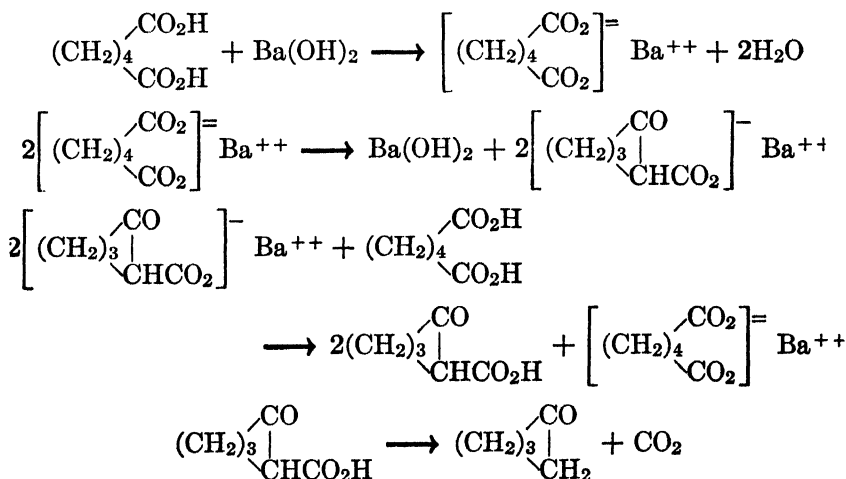
Acetylene itself yields an aldehyde but all other acetylenic compounds are converted to ketones.

### Pyrolysis of Carboxylic Acids and Their Salts

Carboxylic acids or their salts give aldehydes or ketones when decomposed by heat. Acetic acid yields acetone when passed through a hot tube containing manganous oxide.



Similarly, adipic acid may be converted to cyclopentanone by heating with barium hydroxide (p. 136). The mechanism in this case appears to be the following:



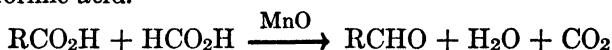
From this it will be seen that only catalytic amounts of barium hydroxide are needed. Actually, 1 mole of adipic acid is converted to cyclopentanone in yields of 80 per cent by use of about  $\frac{1}{20}$  mole of barium hydroxide. Lead salts of acids have been found to give yields as high as 80 to 90 per cent of the corresponding ketones.

This method has been used in the synthesis of large rings (p. 137). The effect of chain length on the tendency of dibasic acids to form cyclic anhydrides or cyclic ketones is expressed by the Blanc rule. It states

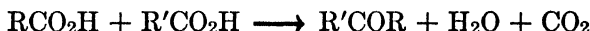


that when adipic and pimelic acids are heated with acetic anhydride and then distilled (at about 300°) cycloalkanones are formed, whereas succinic and glutaric acids under similar conditions yield cyclic anhydrides.

Aldehydes may be made by decomposing a mixture of acids one of which is formic acid.

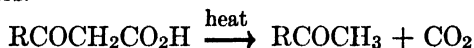


Mixed ketones are also obtained in this way.

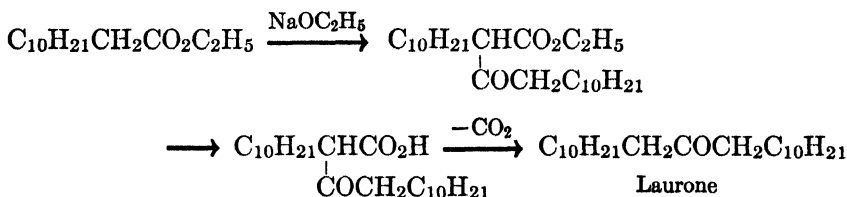


This method has the disadvantage of producing the two symmetrical ketones,  $\text{RCOR}$  and  $\text{R}'\text{COR}'$ , as well as the mixed ketone.

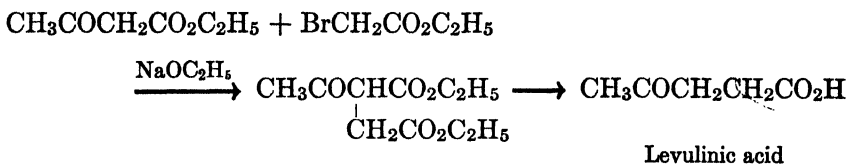
$\beta$ -Keto acids readily decompose into carbon dioxide and the corresponding ketones.



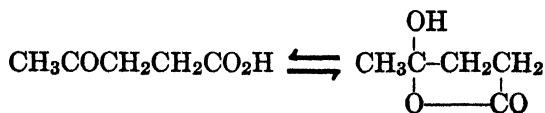
This is a general reaction and is utilized in the synthesis of higher symmetrical ketones. For example, from ethyl laurate it is possible to prepare laurone in good yield.



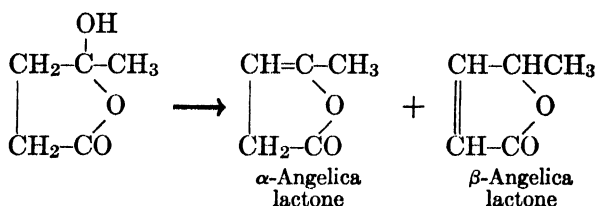
The synthesis of levulinic acid from acetoacetic ester also involves this method.



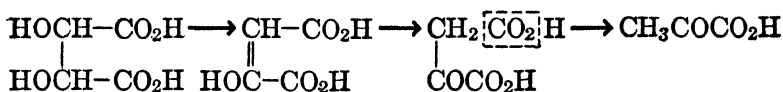
Levulinic acid is generally made from sucrose, glucose, or fructose by the action of dilute sulfuric or hydrochloric acid. This acid has unusual properties. Its reactions indicate that it exists chiefly in the lactol form.



Long heating converts it to *alpha*- and *beta*-angelica lactones.



Pyrolysis of tartaric acid produces a keto acid, pyruvic acid. In this case both water and carbon dioxide are formed.

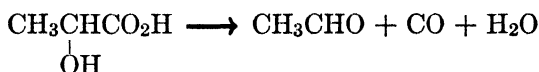


Pyruvic acid can be made also from acetyl bromide through the corresponding keto nitrile. This method gives low molecular weight aliphatic  $\alpha$ -keto acids in yields of 60 per cent.



When citric acid is heated with sulfuric acid it loses water and carbon monoxide to give the corresponding keto acid, acetonedicarboxylic acid (p. 144).

Lactic acid decomposes in a similar manner to form acetaldehyde, carbon monoxide, and water.



These two reactions illustrate a thermal decomposition which is general for  $\alpha$ -hydroxy acids.

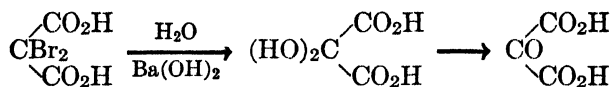
### The Hydrolysis of Dichlorides

Compounds having two halogen atoms on the same carbon atom are hydrolyzed to carbonyl compounds. An example is benzal chloride (p. 233).



The reaction is practically useless in the aliphatic series because the dihalogen compounds are hard to prepare and their hydrolysis requires heating with alkali—a treatment which often causes the products to resinify.

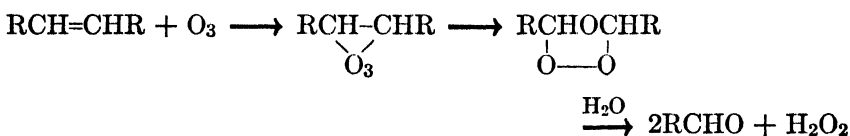
Mesoxalic acid is formed by the hydrolysis of dibromomalonic acid.



Mesoxalic acid shows a remarkable tendency to exist as the hydrate.

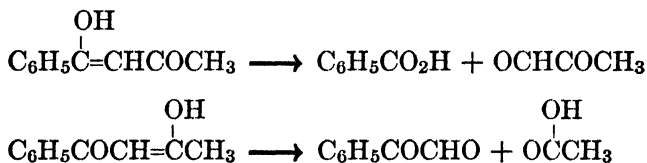
### Ozonization of Olefins

Ozone reacts additively with olefinic compounds to form ozonides which, with water, decompose into carbonyl compounds.



This is not only a method for making aldehydes and ketones but serves also to locate a double bond in a molecule. Thus oleic acid,  $\text{C}_{17}\text{H}_{33}\text{CO}_2\text{H}$ , yields the two aldehydes,  $\text{CH}_3(\text{CH}_2)_7\text{CHO}$  and  $\text{OCH}(\text{CH}_2)_7\text{CO}_2\text{H}$ . This shows that the structure is  $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H}$ . In order to isolate aldehydes it is necessary to carry out the hydrolysis of the ozonide in the presence of a mild reducing agent such as zinc.

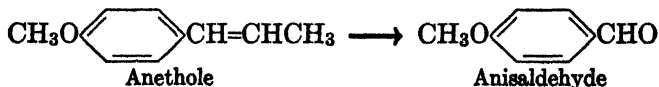
This method can also be used to determine the structure of enols. The ozonization products of the two possible enol forms of benzoylacetone are different and serve to show which form actually occurs.



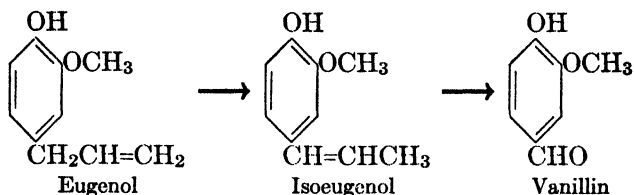
The formation of benzoic acid and methylglyoxal shows the first type of enolization to predominate.

### Oxidation of Olefinic Compounds

Certain aromatic aldehydes are made from naturally occurring substances containing unsaturated side chains. Anisaldehyde, for example, is formed by oxidation of anethole.

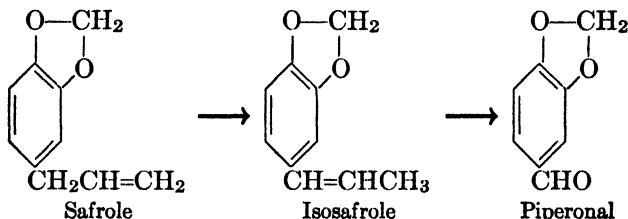


The oxidation may be effected by use of nitric acid, chromic acid, or ozone. Similarly, vanillin can be made from eugenol.



The first step in this process is the rearrangement of eugenol to isoeugenol; this is brought about by heating with alkali and is a general reaction for allylbenzene derivatives. It involves a 1,3 shift of a triad system; in the present example the double bond shifts into a position in which it is conjugated with those of the ring.

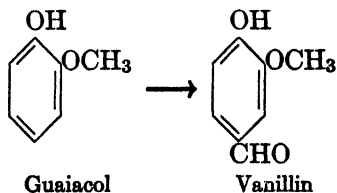
Piperonal is made from safrole in a similar way.



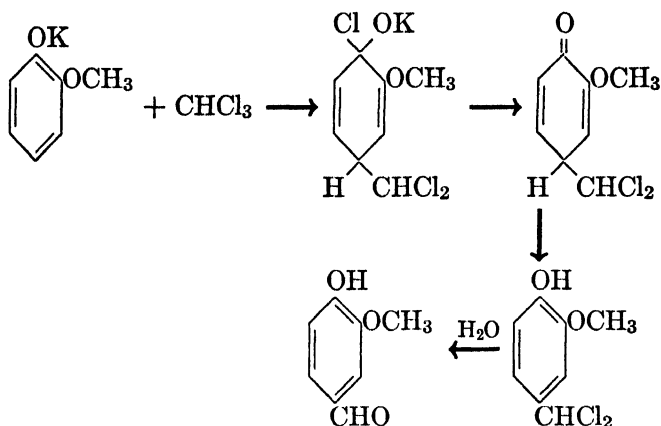
### The Reimer-Tiemann Reaction

Phenols react with chloroform and alkalis to give *o*- and *p*-hydroxy aldehydes (p. 162).

The reaction gives predominantly *ortho* derivatives, but *para* isomers are also formed. The presence of nitro, carboxyl, and other *meta*-directing groups prevents the reaction from taking place. If one *ortho* position is filled the aldehyde group tends to go to the *para* position. An example is the synthesis of vanillin from guaiacol.



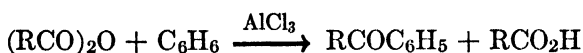
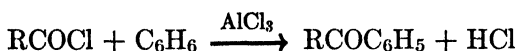
Here the mechanism would appear to involve a 1,4 addition.



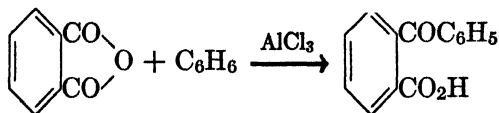
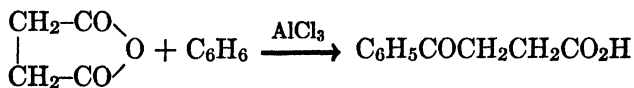
When carbon tetrachloride is used in place of chloroform an exactly similar reaction occurs, the final product being an acid instead of an aldehyde.

### The Friedel-Crafts Reaction

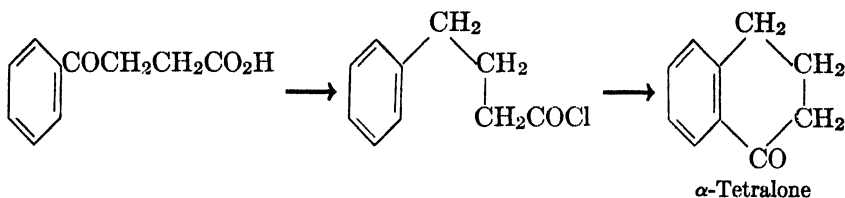
The use of acid chlorides and anhydrides in the Friedel-Crafts reaction (p. 96) is very general.



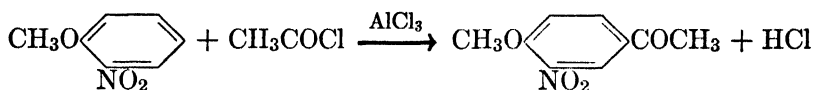
This reaction can be used also with cyclic anhydrides such as succinic and phthalic anhydrides. With benzene they form, respectively,  $\beta$ -benzoylpropionic acid and  $\alpha$ -benzoylbenzoic acid.



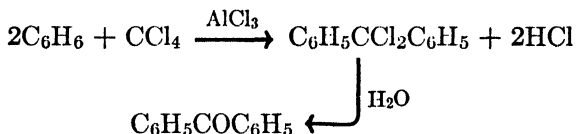
$\beta$ -Benzoylpropionic acid is an intermediate in a synthesis of  $\alpha$ -tetralone. Reduction converts the acid to  $\gamma$ -phenylbutyric acid, the acid chloride of which undergoes cyclization under the influence of aluminum chloride.



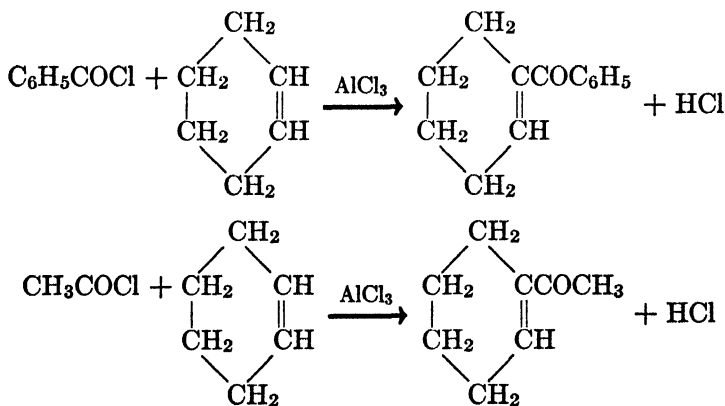
Unsaturated groups such as nitro, keto, sulfonic acid, and cyano generally prevent the Friedel-Crafts reaction from taking place. Nitrobenzene and methyl benzoate, for example, will not react. However, if an activating group is present reaction may proceed. *o*-Nitroanisole, for example, reacts readily.



Benzophenone is made by a Friedel-Crafts condensation between benzene and carbon tetrachloride followed by hydrolysis of the resulting dichloride.

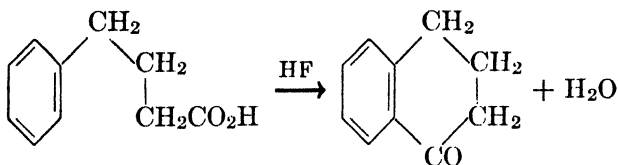


The Friedel-Crafts reaction is not limited to the aromatic series, but can be carried out with olefins also. From cyclohexene and benzoyl or acetyl chloride, good yields of tetrahydrobenzophenone or tetrahydroacetophenone, respectively, may be obtained.



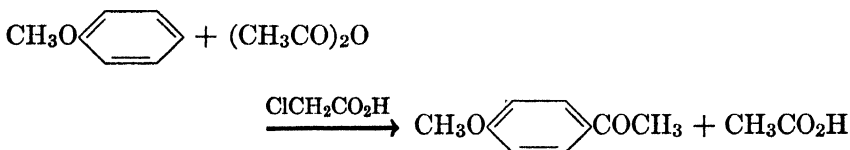
Zinc chloride and ferric chloride are sometimes used in place of aluminum chloride. If boron fluoride is used as the catalyst the acid chloride

or anhydride may be replaced by an acid. Hydrogen fluoride is a superior catalyst for cyclization reactions of this type. For example,  $\gamma$ -phenylbutyric acid is converted to  $\alpha$ -tetralone in 92 per cent yield.

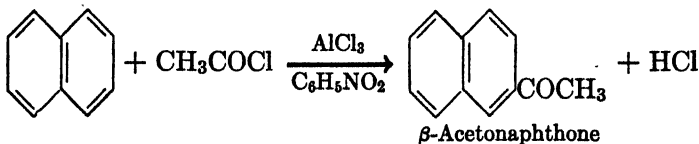


Alkylations and acylations with hydrogen fluoride are carried out in a copper bomb and at moderate temperatures.

A remarkable instance of catalysis has been observed in the formation of *p*-methoxyacetophenone from anisole by treatment with acetic anhydride. The reaction is negligible when the reactants are heated alone, but heating for forty-eight hours at 170–180° in the presence of chloroacetic acid causes the reaction to give yields of 90 per cent.



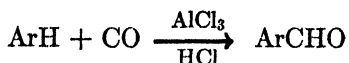
The Friedel-Crafts reaction is generally carried out in the presence of a solvent. If one of the reactants is a liquid hydrocarbon such as benzene it is ordinarily used as a solvent also. Otherwise carbon disulfide is frequently used. Petroleum ether is also employed. Nitrobenzene is useful not only because of its solvent power but also because it forms an addition complex with aluminum chloride and in this way tends to make the action of the latter milder. The course of the reaction is sometimes greatly affected by the solvent. The acylation of naphthalene with acetyl chloride in carbon disulfide gives  $\alpha$ -acetonnaphthone whereas in nitrobenzene the product is the *beta* isomer.



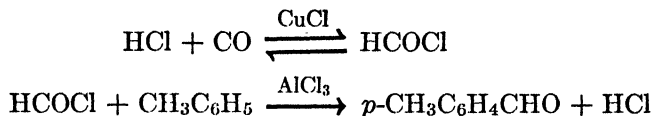
### Gattermann's Methods

Aromatic aldehydes may be made by the use of carbon monoxide, dry hydrogen chloride, aluminum chloride, and an activator such as

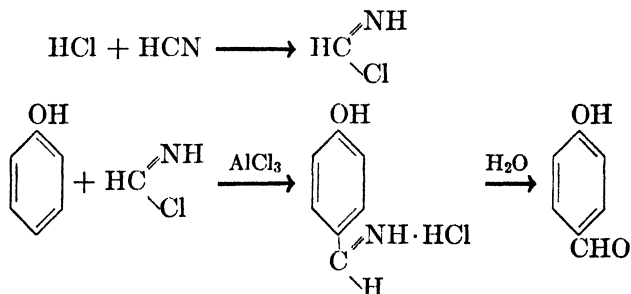
cuprous chloride. The use of pressure eliminates the necessity for an activator.



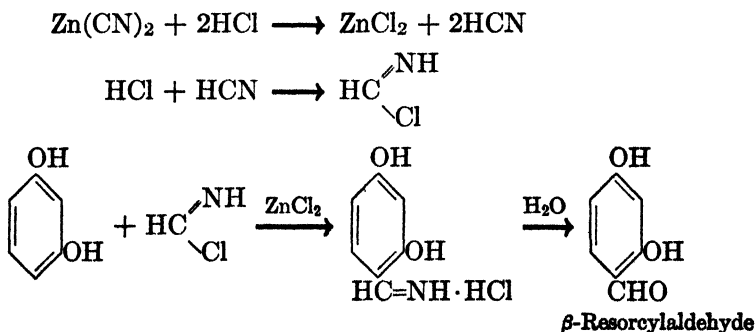
This is known as the Gattermann-Koch reaction. It probably involves the intermediate formation of the unstable formyl chloride, and is to be regarded as a typical example of the Friedel-Crafts reaction. By this method toluene yields 50 to 55 per cent of *p*-tolualdehyde.



A similar method also due to Gattermann involves the use of hydrogen cyanide and hydrogen chloride. In this reaction the unstable imino chloride of formic acid probably is formed as an intermediate. The reaction is useful when phenols are employed.



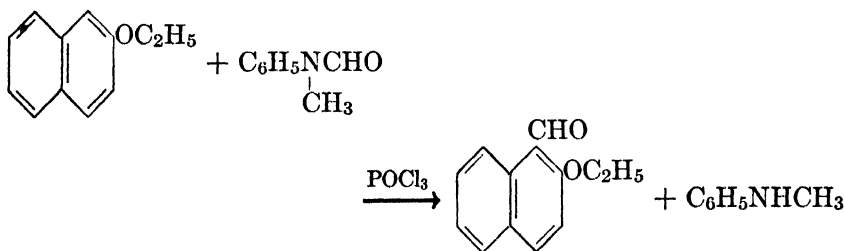
Zinc chloride is often used in place of aluminum chloride when sensitive compounds are involved. The procedure has been improved by substituting zinc cyanide for the anhydrous hydrogen cyanide, which is troublesome to prepare. The interaction of zinc cyanide and hydrogen chloride gives the hydrogen cyanide and zinc chloride needed for the reaction. *β*-Resorcyraldehyde, for example, may be made conveniently in this way.





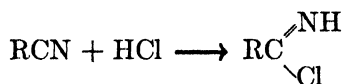
Recently it has been shown that when pure zinc cyanide is used the reaction fails to take place. Satisfactory results are obtained, however, if small amounts of sodium or potassium chloride are added to the zinc salt.

A method which is formally somewhat similar involves the interaction of formylmethylaniline and aromatic compounds possessing highly active nuclear hydrogen atoms. The synthesis of 2-ethoxy-1-naphthaldehyde is an example.

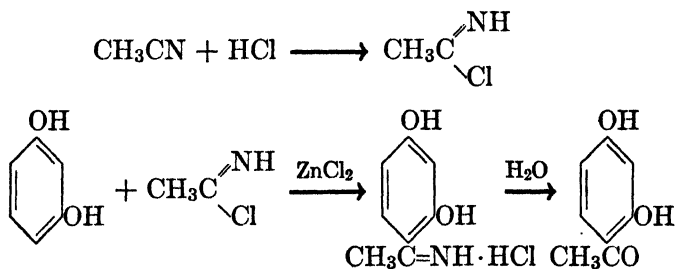


### The Houben-Hoesch Synthesis

Another method which is really a variation of the Friedel-Crafts synthesis is the Houben-Hoesch process; it consists in the condensation of nitriles with phenols in the presence of hydrogen chloride and zinc chloride. Here again an imino chloride is probably formed as an intermediate.



The synthesis of resacetophenone from resorcinol will serve as an example.

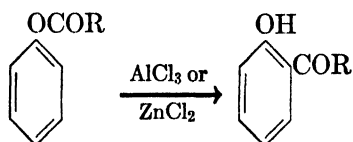


This is a general reaction for nitriles and phenols.

### The Fries Rearrangement

\* Phenyl esters and substituted phenyl esters rearrange to the corresponding *ortho* and *para* acyl phenols when heated with aluminum or

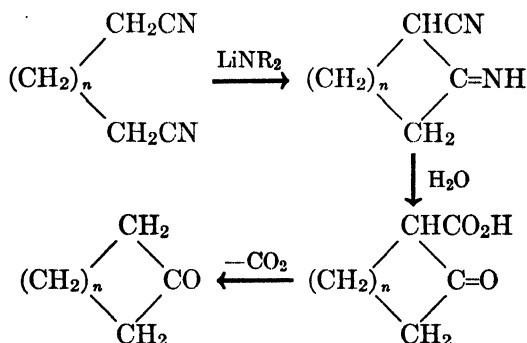
zinc chloride. This is known as the Fries rearrangement, but the process is probably not a true rearrangement. The mechanism may involve scission of the molecule into an acid chloride and phenol—compounds which react normally to give the keto phenol.



Phenyl propionate yields 45 to 50 per cent of *p*-propiophenol and 32 to 35 per cent of the *ortho* isomer.

### Ziegler's Method

One of the most successful methods of making cyclic ketones of many members is due to Ziegler, who used the Thorpe reaction to close rings. He found that certain dinitriles could be caused to condense intramolecularly to give imino nitriles which by hydrolysis and decarboxylation yield cyclic ketones. The catalyst is an alkali metal derivative of a secondary amine.

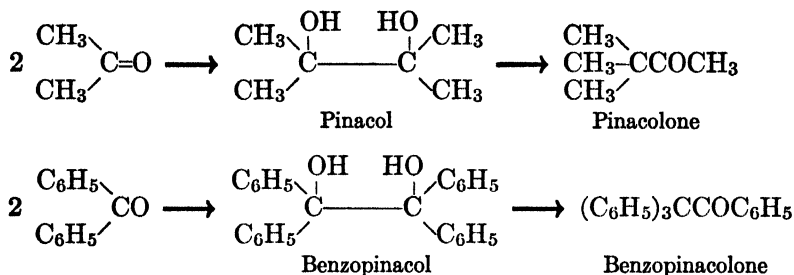


Yields as high as 50 per cent are obtained in the synthesis of cyclopentadecanone—a compound which is an important artificial musk.

### The Pinacol-Pinacolone Rearrangement

Ditertiary 1,2-glycols—generally obtained by bimolecular reduction of ketones—are known as pinacols. When treated with acids they undergo rearrangement to ketones known as pinacolones. Acetone and

benzophenone, for example, yield pinacolone and benzopinacolone, respectively.



### Selenium Dioxide Oxidation

Active methyl and methylene groups are converted, respectively, to aldehyde and ketone groups by the action of selenium dioxide. Acetone and acetophenone yield, respectively, methylglyoxal and phenylglyoxal.

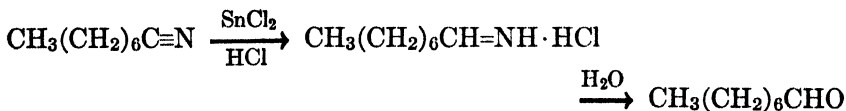


### The Grignard Method

The synthesis of aldehydes and ketones by use of the Grignard reagent has been discussed (p. 266).

### Stephen's Method

Nitriles are reduced by stannous chloride in the presence of hydrogen chloride to give imine hydrochlorides. These yield aldehydes when hydrolyzed. The synthesis of *n*-octaldehyde is an example.



This method has been reported to give high yields of myristaldehyde, palmitaldehyde, stearaldehyde, benzaldehyde,  $\beta$ -naphthaldehyde, *m*-tolualdehyde, and *p*-tolualdehyde. *o*-Tolunitrile and  $\alpha$ -naphthonitrile give low yields, presumably because of steric hindrance.

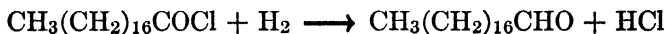
Stephen's method for the higher aliphatic aldehydes takes on renewed interest in view of the fact that certain of the higher nitriles are now made commercially from fats.

### Sommelet's Method

Aromatic aldehydes can be made from the corresponding hydrocarbons by chloromethylation followed by treatment of the chloromethyl derivative with hexamethylenetetramine. This method, discovered by Sommelet, has found little application. The chloromethyl compound condenses with the tetramine to give a quaternary ammonium chloride. Heating the latter in aqueous alcohol decomposes it into the aldehyde and other products.  $\alpha$ -Naphthaldehyde can be made in yields of 60 per cent by this method.

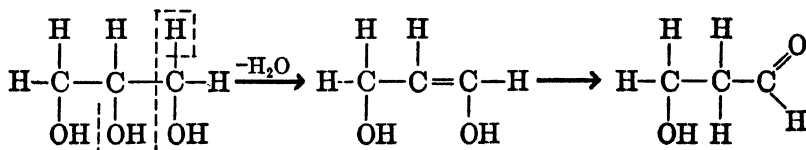
### Rosenmund's Method

Aldehydes which are obtainable only with difficulty may be made by catalytic reduction of the corresponding acid chlorides according to the procedure of Rosenmund. A palladium catalyst is deposited on freshly precipitated barium sulfate. By this method stearaldehyde, for example, is made from stearyl chloride.

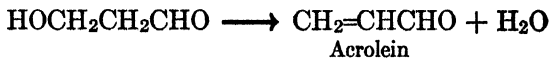


### Special Methods

**Acrolein.** Acrolein is made by heating glycerol with potassium acid sulfate. The loss of two molecules of water probably occurs in the following steps. The secondary hydroxyl group would be expected to split off more readily than the primary ones.

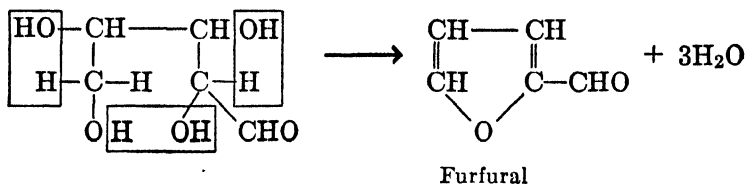


The enol would ketonize to give the  $\beta$ -hydroxy aldehyde—a type of substance which readily loses water.



Acrolein is prepared commercially by the catalytic oxidation of allyl alcohol.

**Furfural.** Furfural, an important aldehyde, is obtained by hydrolysis of pentosans. Substances such as corn cobs, wheat straw, or bran are digested with hydrochloric acid; under these conditions the liberated pentoses are transformed into furfural.



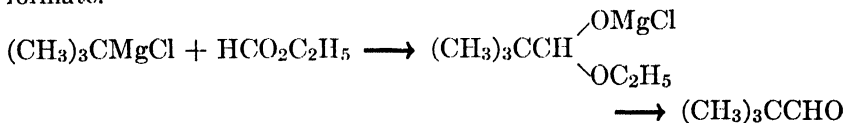
Furfural is produced commercially from oat hulls.

**Chloral.** Chloral is made by the chlorination of ethyl alcohol with dry chlorine.



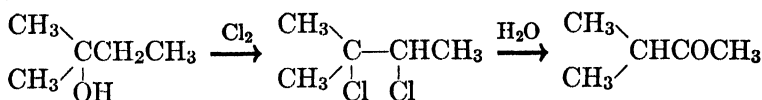
**Acetone.** Acetone is manufactured by fermentation of molasses or of starch from corn (p. 49).

**Trimethylacetaldehyde.** Trimethylacetaldehyde is best made by the condensation of *t*-butylmagnesium chloride with an excess of ethyl formate.

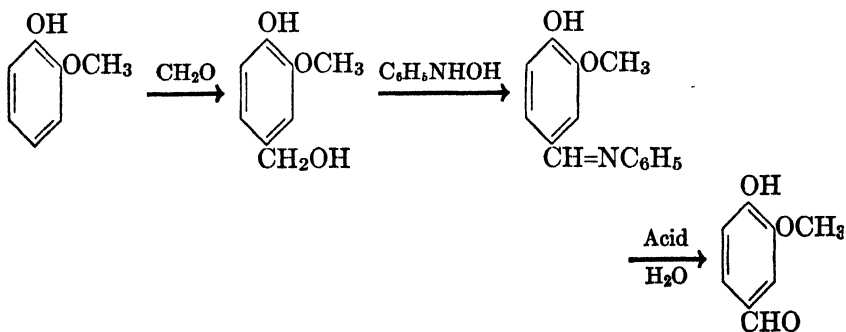


This is an interesting illustration of the influence of steric hindrance. The aldehyde is less reactive than the formate. Even if the Grignard reagent reacts with the aldehyde it does so by reduction, not by addition.

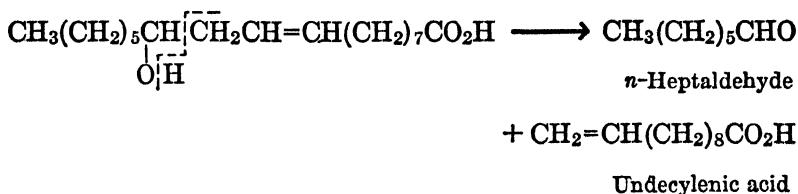
**Methyl Isopropyl Ketone.** Methyl isopropyl ketone is made commercially by the rearrangement and hydrolysis of trimethylethylene bromide or chloride. The latter can be made by direct halogenation of *t*-amyl alcohol.



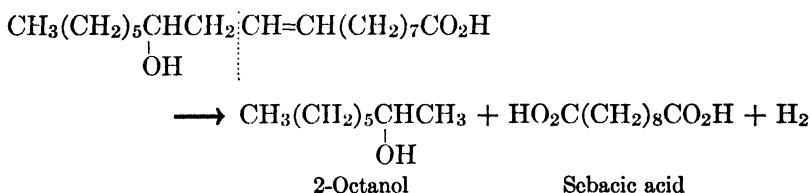
**Vanillin.** Vanillin is commonly made from guaiacol by the following steps:



***n*-Heptaldehyde.** *n*-Heptaldehyde is formed in yields of 60 per cent by the destructive distillation of castor oil under reduced pressure. Castor oil is made up largely of the glyceride of ricinoleic acid, which, under the influence of heat, breaks down to give *n*-heptaldehyde and undecylenic acid.

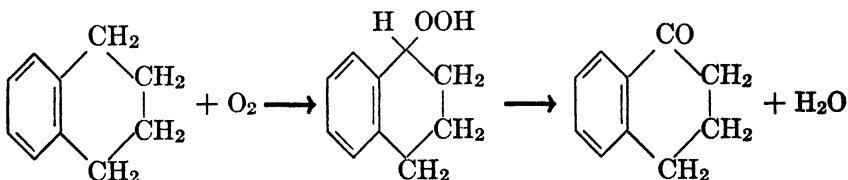


It is interesting to note that alkali cleaves the chain at a different point to give 2-octanol, sebacic acid, and hydrogen (p. 133).

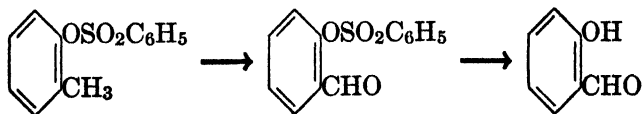


**Cinnamaldehyde.** Cinnamaldehyde is obtained from cinnamon oil by extraction with sodium bisulfite.

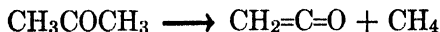
**$\alpha$ -Tetralone.**  $\alpha$ -Tetralone (p. 286) is best prepared by passing air through tetralin at about 70° for fifty to fifty-five hours, and decomposing the resulting peroxide with dilute sodium hydroxide.



**Salicylaldehyde.** A technical method for the manufacture of salicylaldehyde consists in the oxidation of *o*-cresyl benzenesulfonate with manganese dioxide in sulfuric acid solution. Hydrolysis of the resulting ester gives the phenolic aldehyde.

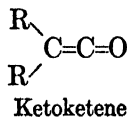
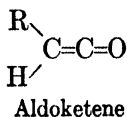


**Ketenes.** Carbonyl compounds which contain the grouping  $>\text{C}=\text{C}=\text{O}$  are known as ketenes. The simplest member of the series, ketene, is prepared by thermal decomposition of acetone.

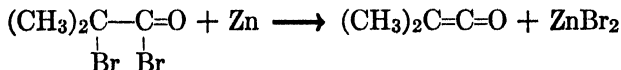


In the laboratory excellent yields are obtained by passing acetone vapors over an electrically heated metal filament at  $700\text{--}750^\circ$ .

Other ketenes fall into two classes, aldoketenes and ketoketenes.

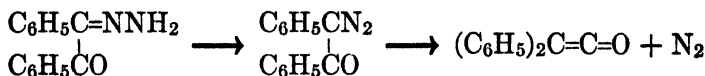


The most general method of synthesis involves debromination of  $\alpha$ -bromoacyl bromides by the action of zinc. Dimethylketene, for example, is made in this way.

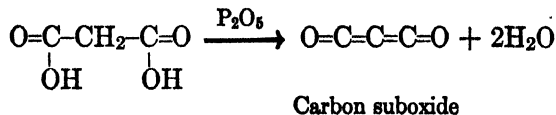


Ketene dimerizes to acetylketene which is used in the synthesis of acetoacetic esters.

Diphenylketene, the ketene which has been studied most carefully, is most readily obtained by a special method. Benzil monohydrazone is oxidized by mercuric oxide to azibenzil and the latter is decomposed thermally.



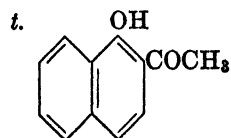
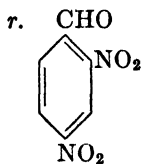
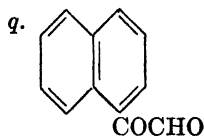
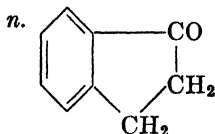
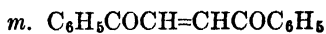
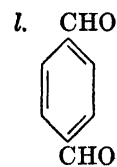
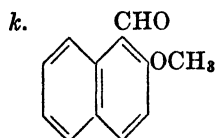
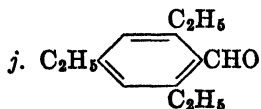
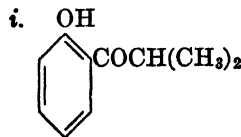
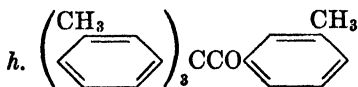
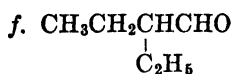
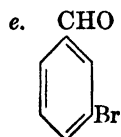
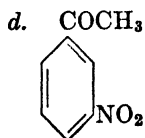
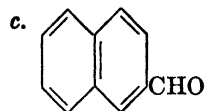
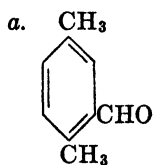
The "twinned" double bond structure characteristic of ketenes is present also in carbon suboxide, a dehydration product of malonic acid.



Carbon suboxide reacts with water and alcohol to give, respectively, malonic acid and ethyl malonate.

PROBLEM

Indicate methods that might be used in the synthesis of the following aldehydes and ketones.





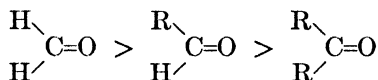
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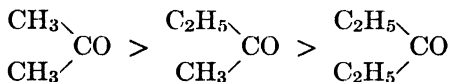
## CHAPTER XXII

### REACTIONS OF THE CARBONYL GROUP

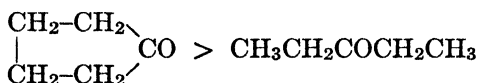
The order of reactivity of carbonyl compounds seems to be determined by the size and complexity of the radicals to which the carbonyl group is attached. Thus the following is the order of decreasing activity.



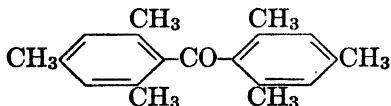
Methyl ketones are more reactive than their higher homologs.



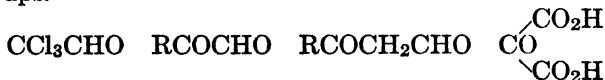
Also, cyclic ketones are more reactive than their open-chain analogs.



When the radicals are very large and complex the carbonyl group may become almost entirely inert. Dimesityl ketone is an example.

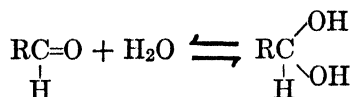


Negative atoms and groups often enhance the reactivity of carbonyl compounds. The following, for example, possess unusually reactive carbonyl groups.



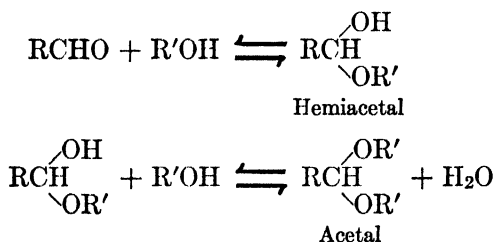
### Transformations of the Carbonyl Group

**Water.** Only extremely reactive carbonyl compounds form hydrates which can be isolated, but it is probable that the tendency is characteristic of all aldehydes and perhaps of ketones also.



Chloral forms a hydrate whose structure is known to be  $\text{Cl}_3\text{CCH}(\text{OH})_2$ . Glyoxals react similarly:  $\text{RCOCHO} + \text{H}_2\text{O} \longrightarrow \text{RCOCH}(\text{OH})_2$ . There is good reason to believe that formaldehyde is hydrated in water solution. The partial pressure of the aldehyde over its aqueous solution is far less than one would expect.

**Alcohols.** As was stated earlier (p. 70), aldehydes react with alcohols to form hemiacetals and these in turn are converted to acetals (p. 70).



The rate of acetalization depends on the nature of the aldehyde as well as that of the alcohol. Aromatic aldehydes react rapidly but give low yields on account of an unfavorable equilibrium. Many aliphatic aldehydes afford excellent yields, but the reaction is slower. The examples given in Table XXIX illustrate these points.

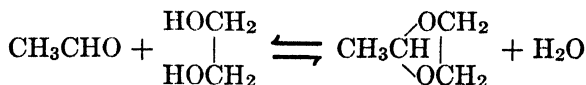
TABLE XXIX

## ACETALS

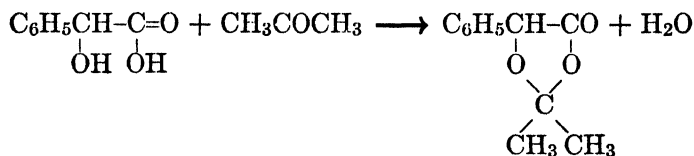
Acetal	Amount of Acetal at Equilibrium	Reaction Rate Constant
Methyl butyral	96.4%	$0.83 \times 10^{-3}$
Methyl acetal	93.8	1.02
Ethyl acetal	90.7	2.37
Ethyl isobutyral	83.5	1.56
<i>t</i> -Butyl acetal	31.2	11.34
Ethyl benzal	36.3	Ca 100
Ethyl <i>m</i> -nitrobenzal	41.8	Ca 200

Calcium chloride is a better catalyst for acetal formation than is zinc or ferric chloride. Boron trifluoride and ammonium chloride are also useful catalysts.

Cyclic acetals or dioxolanes are formed by glycols.

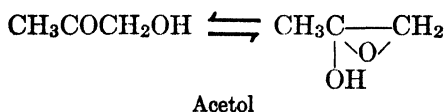
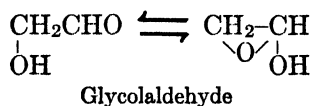


$\alpha$ -Hydroxy acids are 1,2-dihydroxy compounds and, like 1,2-glycols, are capable of forming cyclic acetone derivatives. Mandelic acid, for example, combines with acetone under the influence of sulfuric acid to yield a dioxolone.



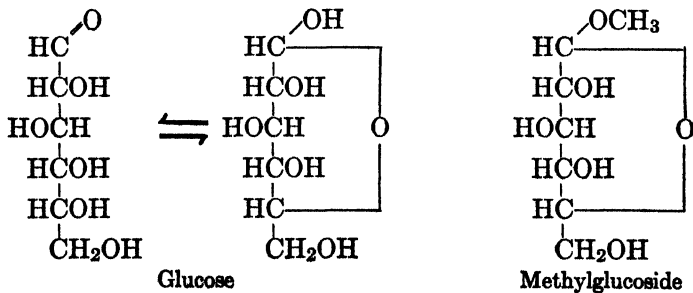
The dioxolone is closely related to esters and acetals. When treated with liquid ammonia it yields mandelamide.

Hydroxy aldehydes and ketones in which the two groups are not too far apart show a tendency to form cyclic hemiacetals. Glycolaldehyde and acetol are examples.

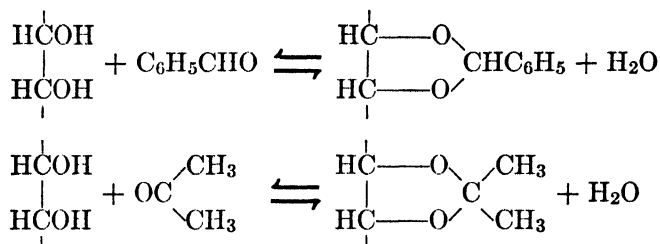


This behavior is more marked in  $\gamma$ - and  $\delta$ -hydroxy aldehydes and ketones which give rings of five and six members, respectively.

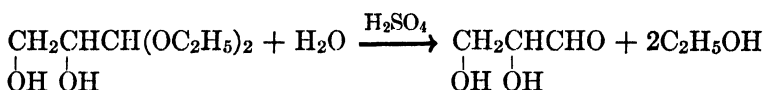
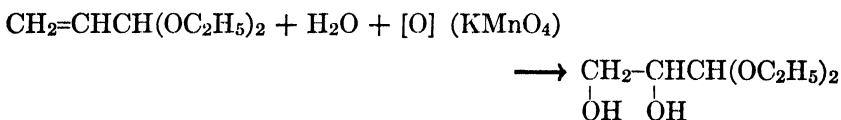
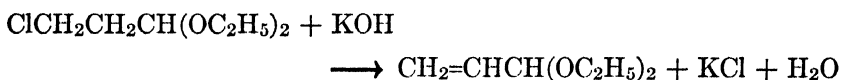
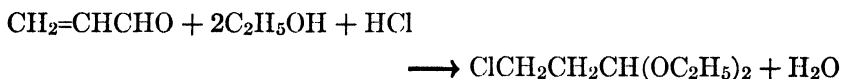
These reactions are especially important in sugar chemistry. The ring forms written for glucose and methylglucosides represent, respectively, a hemiacetal and an acetal.



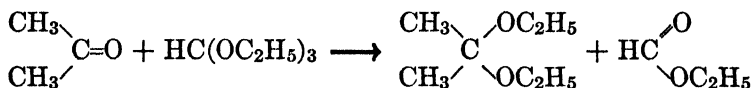
Of use also in sugar chemistry is the formation of cyclic acetals and ketals with benzaldehyde and acetone.



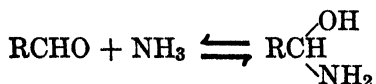
Acetals are sensitive to acids but are unattacked by alkalis. Advantage is taken of the latter property to protect aldehyde groups. Aldehydes cannot be handled in contact with alkalis or oxidizing agents. The problem can be solved by converting them to acetals from which they can be regained at a later point in the synthesis. The preparation of glyceraldehyde from acrolein illustrates this device.



Ketones form acetals but react less readily than do aldehydes; for this reason, ketals are generally made by treating the ketones with an orthoformic ester.



**Amino Compounds.** Like water and alcohols, amino compounds react with aldehydes to give addition compounds. Ammonia gives rise to the aldehyde ammonias (p. 71).



Like the corresponding hydrates and alcoholates the aldehyde-ammonias are unstable, being readily broken down to ammonia and the aldehydes. They are useful in the purification of aldehydes.

Primary and secondary amines add to formaldehyde to produce methanol derivatives which are stable.



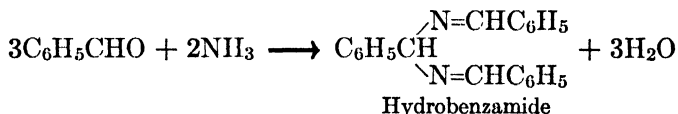
Carbonyl compounds which have a marked tendency to enolize react with ammonia and amines to yield nitrogen derivatives which may be formulated as imines or amines.



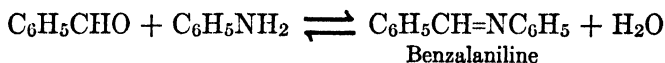
Evidence favors the latter structure.

The exceptional behavior of formaldehyde with ammonia has already been mentioned (p. 67).

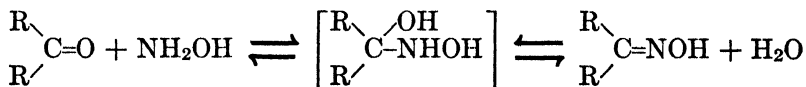
Benzaldehyde does not give a simple addition compound with ammonia but a complex molecule, hydrobenzamide, formed from three molecules of aldehyde and two of ammonia.



Hydrobenzamide is related to Schiff bases, substances formed by the interaction of aldehydes and primary amines. Benzalaniline is an example.



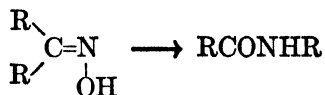
Hydroxylamine probably reacts in the same way as ammonia, but in this case water is eliminated and oximes result (p. 72).



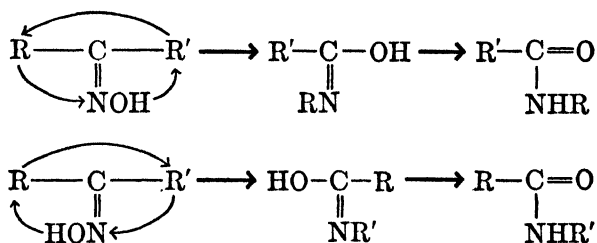
This reaction is reversible. It is general for aldehydes and ketones.

The oximes of aldehydes and unsymmetrical ketones exist in *syn* and *anti* forms which correspond to *cis-trans* isomers. In most instances the configurations of oximes of ketones have been assigned on the basis of the products obtained by subjecting them to the action of certain acidic reagents such as phosphorus pentachloride in ether. An isomerization known as the Beckmann rearrangement occurs. The products are

amides, and the reaction of a symmetrical ketoxime can be represented as follows:

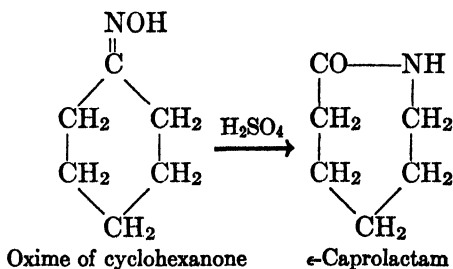


If the ketoxime is unsymmetrical two products,  $\text{R}'\text{CONHR}$  and  $\text{RCONHR}'$ , might be expected. Actually one of these is obtained from the *syn* oxime and the other from the *anti* oxime. The course of this rearrangement has been studied with great care, and it is now known that the shift of groups is *trans* rather than *cis*. The following scheme has been used to represent the sequence of changes.

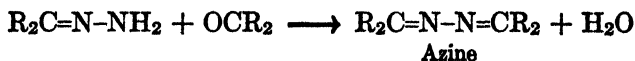
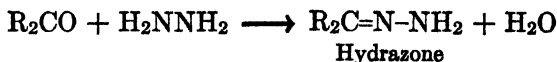


The Beckmann rearrangement is useful in determining the structure of ketones. Hydrolysis of the amide gives an acid and an amine; from these the structure of the original ketone is deduced.

Occasionally this rearrangement is of value in synthetic work. An interesting example is the synthesis of  $\epsilon$ -aminocaproic acid from the oxime of cyclohexanone. The first step involves the Beckmann rearrangement which transforms the oxime into  $\epsilon$ -caprolactam.

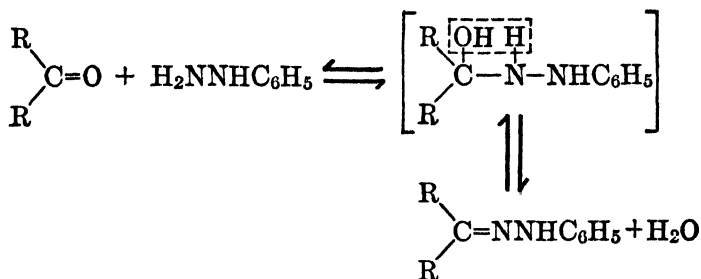


Hydrazine reacts with aldehydes and ketones to give hydrazones which in turn may react with a second molecule of the carbonyl compound to yield azines.

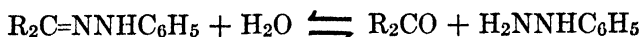


Aliphatic aldehydes react so rapidly that the intermediate hydrazones cannot be isolated; even by use of an excess of hydrazine the azine is practically the only product. Hydrazones of ketones tend to change to the azine and free hydrazine.

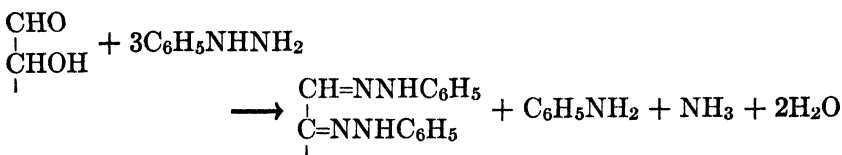
Phenylhydrazine reacts to give phenylhydrazones (p. 72).



The reversibility is illustrated by one of the methods of recovering the carbonyl compounds from the hydrazone. This consists in heating the phenylhydrazone with a carbonyl compound such as a glyoxal which is highly reactive.

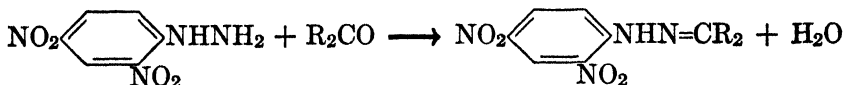


$\alpha$ -Hydroxy aldehydes and ketones react with phenylhydrazine to give phenylosazones.



These are yellow solids which crystallize well and are of great value in the purification and characterization of sugars.

2,4-Dinitrophenylhydrazine is much used in identification work because the 2,4-dinitrophenylhydrazones are generally solid.



$\beta$ -Diketones and  $\beta$ -keto esters yield phenylhydrazones but the reaction goes farther and gives cyclic products. Acetylacetone, for example yields 1-phenyl-3,5-dimethylpyrazole.



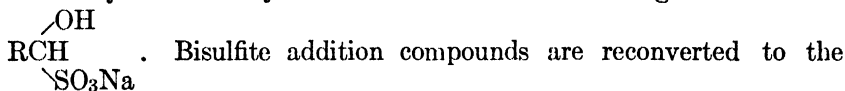


Table XXX shows the amounts of bisulfite addition compounds formed at the end of twenty and seventy minutes.

TABLE XXX  
BISULFITE ADDITION COMPOUNDS

	Per Cent Bisulfite Compound	
	20 min.	70 min.
Acetaldehyde	86.6	88.7
Acetone	39.7	58.9
Methyl ethyl ketone	22.5	38.4
Methyl propyl ketone	11.0	25.5
Methyl isopropyl ketone	5.4	13.0
Pinacolone	5.6	5.6

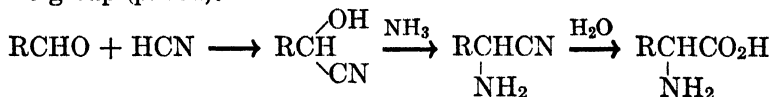
The bisulfite addition compounds of formaldehyde and of acetaldehyde have been proved to be the hydroxy sulfonates, i.e., the sulfur atom is joined directly to carbon as indicated in the general formula



aldehydes or ketones by either acids or bases.

**Hydrogen Cyanide.** Hydrogen cyanide reacts additively with aldehydes and many ketones to give cyanohydrins (p. 70). The reaction is general for aldehydes but is limited in the ketone series. Cyanohydrins are formed by acetone, diethyl ketone, and pinacolone, but not by diisopropyl ketone. The rate of addition is often greatly increased by the presence of a trace of a base such as ammonia, piperidine, or quinoline.

The Strecker synthesis of amino acids involves a combination of this reaction with another in which the hydroxyl group is replaced by an amino group (p. 182).

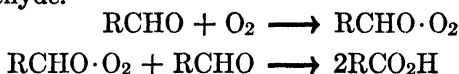


The condensation is carried out by treating an aldehyde with ammonium chloride and sodium cyanide.

**The Grignard Reagent.** The addition of the Grignard reagent to carbonyl compounds has already been discussed. The Reformatsky reaction mentioned earlier is very similar.

**Oxidizing Agents.** Aldehydes are readily oxidized. The Fehling, Tollens, and Benedict tests for aldehydes are based on this property (p. 68). One industrial synthesis of acetic acid involves air oxidation of acetaldehyde in the presence of manganous oxide (p. 23).

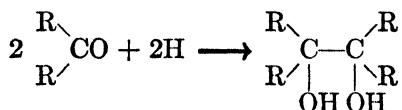
Many aldehydes undergo oxidation merely by standing in contact with the air. This is called autoxidation. The aldehyde first takes up a molecule of oxygen to give a moloxide which then reacts with a second molecule of aldehyde.



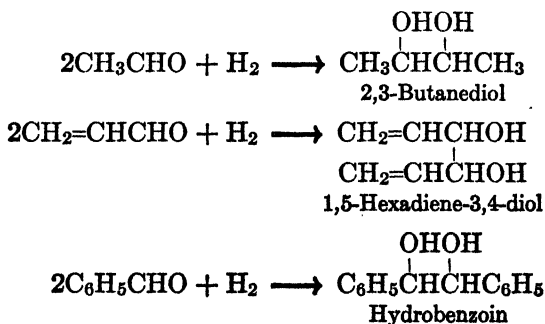
Autoxidation is prevented by the presence of certain substances known as antioxidants. Hydroquinone is commonly used for this purpose. There is evidence also that autoxidation is catalytic; pure benzaldehyde, for instance, does not undergo autoxidation. Autoxidation is often accompanied by chemiluminescence.

**Reducing Agents.** Aldehydes, ketones, and esters are all capable of being reduced but differ widely in the conditions necessary to bring about the reaction. Certain methods of reduction deserve special mention.

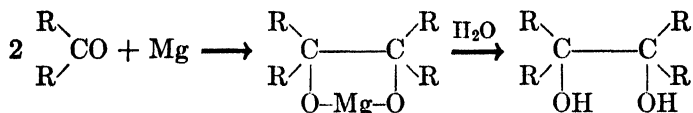
Under suitable conditions aldehydes and ketones may be hydrogenated to give the corresponding alcohols. The usual catalysts are platinum and nickel. Bimolecular reduction is also possible; the products are glycols. This type of reduction is characteristic of ketones and yields pinacols.



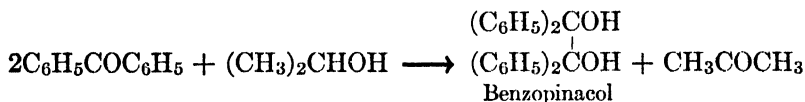
It is of theoretical interest that bimolecular reduction of aldehydes is also possible. Saturated aldehydes give only traces of glycols but  $\alpha,\beta$ -unsaturated aldehydes and aromatic aldehydes undergo this type of reduction more readily. Acetaldehyde, acrolein, and benzaldehyde give, respectively, 2,3-butanediol, 1,5-hexadiene-3,4-diol and hydrobenzoin.



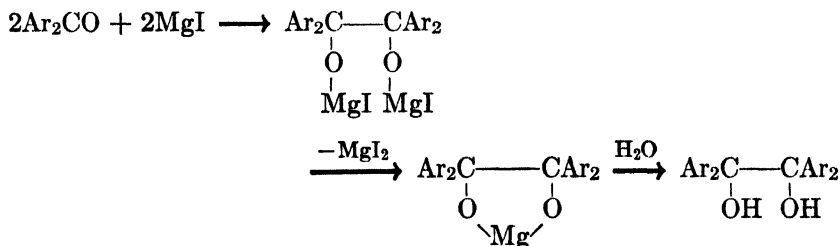
Amalgamated magnesium is used frequently to produce pinacols.



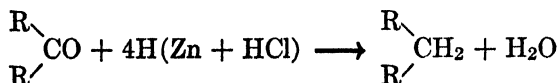
Benzopinacol can be made conveniently by photochemical reduction. Benzophenone is dissolved in isopropyl alcohol and the solution exposed to sunlight. Benzopinacol and acetone are formed.



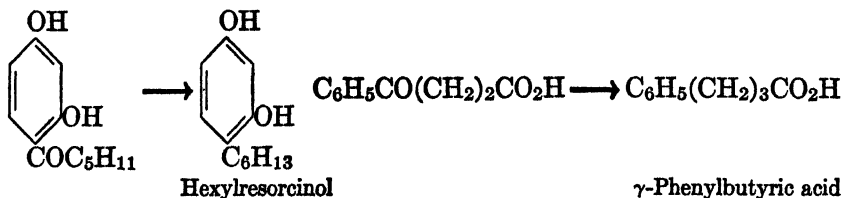
The most convenient general method for reducing benzophenones to pinacols is by the use of the binary mixture,  $\text{Mg} + \text{MgI}_2$ . The latter behaves as though it were magnesian iodide.



Zinc and hydrochloric acid reduce a carbonyl group to a methylene group. This is the Clemmensen method.

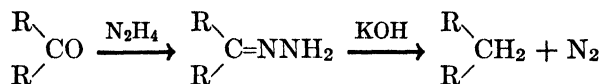


It is especially useful in the introduction of saturated side chains into aromatic compounds. Hexylresorcinol and  $\gamma$ -phenylbutyric acid are examples. The ketones are readily available by the Friedel-Crafts method.



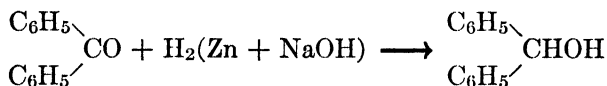
Aldehydes and ketones may also be reduced to the corresponding hydrocarbons by the Wolff-Kishner method. The hydrazone is first formed

and then decomposed catalytically by heating in a closed tube with potassium ethoxide or hydroxide. The sequence of reactions is as follows:

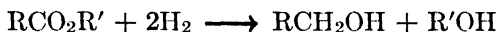


The reaction is of wide application; it usually gives good results with aldehydes, ketones, cyclic ketones, keto acids, and unsaturated carbonyl compounds.

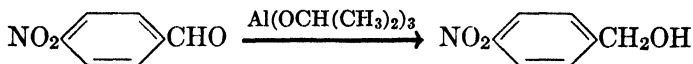
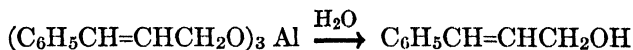
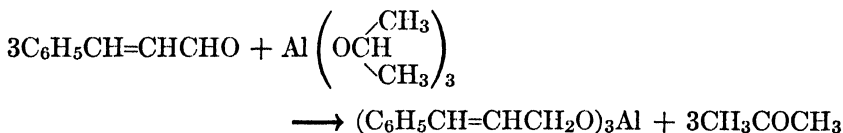
Zinc in the presence of aqueous sodium hydroxide is useful in reducing ketones to secondary alcohols. Thus benzophenone yields benzohydrol.



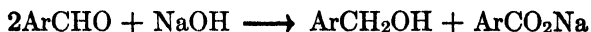
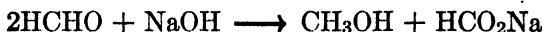
Esters may be reduced to primary alcohols either by sodium and alcohol or by catalytic hydrogenation.



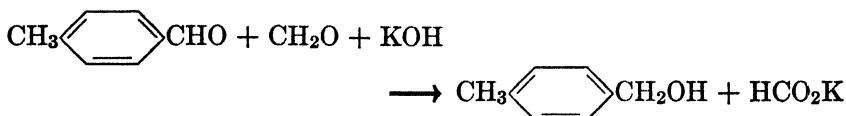
Aluminum isopropoxide is a good reducing agent and seems to be specific for the carbonyl group. Ethylenic linkages, nitro groups, and other unsaturated groupings are unaffected. The reduction of cinnamaldehyde and *p*-nitrobenzaldehyde may be cited by way of illustration.



**The Cannizzaro Reaction.** The Cannizzaro reaction (p. 74) involves both reduction and oxidation. When an aromatic aldehyde or formaldehyde is heated with alkali the corresponding alcohol and acid (as salt) are formed in equal amounts.

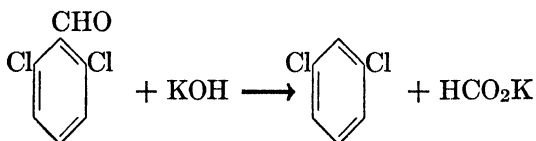


Advantage is taken of this in preparing certain benzyl alcohols by using formaldehyde and an aromatic aldehyde together. This is called a "crossed" Cannizzaro reaction.

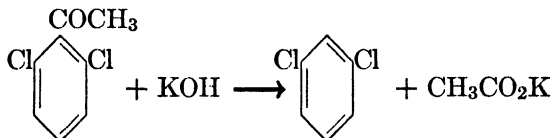


The Cannizzaro reaction also occurs with other aliphatic aldehydes, though much less generally. *n*-Butyraldehyde and *n*-valeraldehyde, for example, undergo this reaction completely when heated with aqueous barium hydroxide for fourteen hours at 150°.

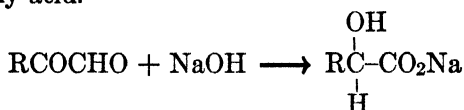
Exceptional behavior is encountered with benzaldehyde derivatives in which the two *ortho* positions are occupied by chlorine, bromine, iodine, or fluorine. In these cases the aldehyde group is eliminated as formic acid. Nitro groups produce the same effect.



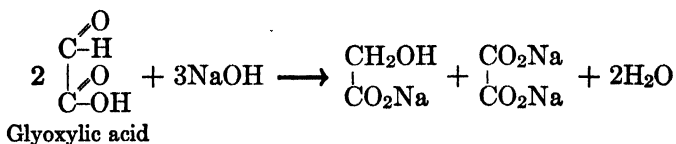
Similarly 50 per cent potassium hydroxide solution cleaves 2,6-dichloroacetophenone to potassium acetate and *m*-dichlorobenzene.



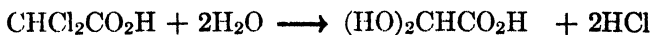
$\alpha$ -Keto aldehydes when treated with alkali undergo a reaction which is essentially an *intramolecular* Cannizzaro reaction. The product is the salt of a hydroxy acid.



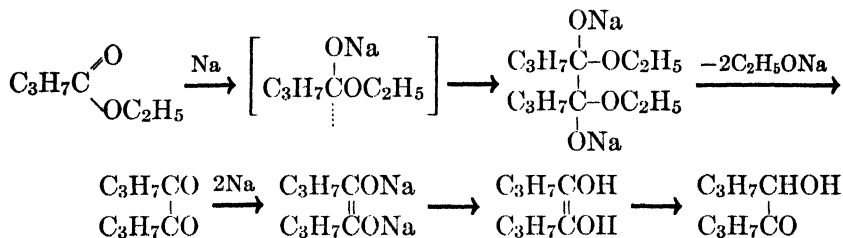
Glyoxylic acid likewise undergoes the Cannizzaro reaction. The products are sodium oxalate and sodium glycolate.



Glyoxylic acid is the simplest aldehyde acid. It can be made by the hydrolysis of dichloroacetic acid. It is of especial interest because it exists as the hydrate. This is true of the free acid and of its salts as well



**Acyloin Formation.** In ether solution esters react with sodium to give acyloins. The mechanism seems to involve the formation of a free radical which dimerizes; the dimer loses sodium alkoxide to give the  $\alpha$ -diketone. The latter is reduced by metallic sodium to the enediolate. The free enediol (p. 194) rearranges to the acyloin. By this method butyrolin, for example, may be made in 80 per cent yields.

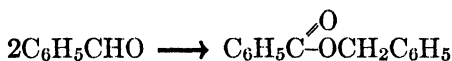


The method is general for esters; propionoin, isobutyrolin, and pivaloin can be made in yields of 55, 75, and 60 per cent, respectively.

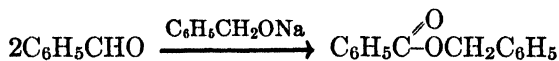
By using xylene or toluene as solvent to obtain higher reaction temperatures and consequent greater solubility of the sodium derivatives the method has been extended successfully to the synthesis of acyloins from twelve to thirty-six carbon atoms. The yields of all are high.

Glycolaldehyde or formoin is the simplest acyloin. Acetoin is available commercially, being made by a special fermentation process.

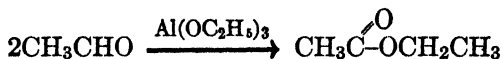
**The Tishchenko Reaction.** It was suggested by Tishchenko that the Cannizzaro reaction involves intermediate formation of an ester.



In the presence of alkali the ester would, of course, be saponified. If sodium benzoxide is used the ester is the chief product.



In general, aldehydes may be converted to esters under the influence of metal alkoxides. For example, acetaldehyde in the presence of aluminum ethoxide yields ethyl acetate.

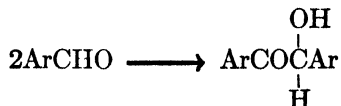


This is known as Tishchenko's method and is general. However, it has found little use because the catalyst soon becomes "poisoned" and loses its activity.

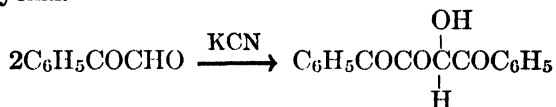
Catalytic hydrogenation is widely used in reducing carbonyl compounds to alcohols. Other useful procedures involve tin and hydro-

chloric acid, sodium amalgam, iron and acetic acid, aluminum amalgam, and electrolytic methods.

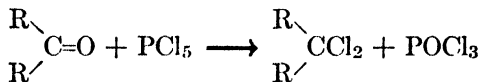
**Potassium Cyanide: The Benzoin Condensation.** Aromatic aldehydes dimerize under the influence of an alkali cyanide to give benzoin.



This is a general reaction of great importance. It is not limited to aromatic aldehydes but takes place with certain aliphatic aldehydes such as phenylglyoxal.

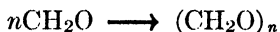


**Phosphorus Pentachloride.** This reagent converts aldehydes and ketones to the corresponding dichloro derivatives.



This reaction is general but finds little use. Its application in the synthesis of acetylenic compounds already has been noted.

**Polymerization.** Polymerization is characteristic of aldehydes. Formaldehyde, for example, forms paraformaldehyde or polyoxymethylene.

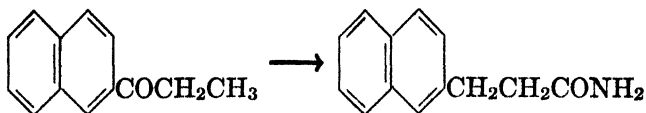


The formula of the polymer is represented as follows.



Ring formation often halts polymerization. Acetaldehyde gives a liquid trimer, paraldehyde (p. 75). Metaldehyde, a solid tetramer of acetaldehyde, is apparently also a ring compound. Neither the trimer nor the tetramer reduces Fehling's solution. Both revert to acetaldehyde when heated.

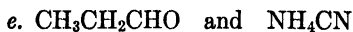
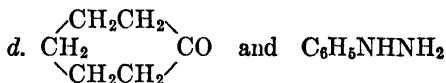
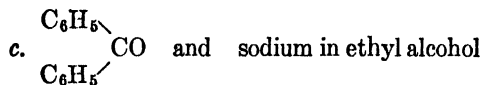
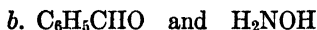
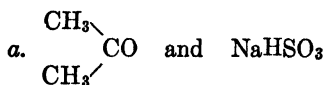
**The Willgerodt Reaction.** Willgerodt found that alkyl aryl ketones could be converted to the amides of the corresponding  $\omega$ -aryl fatty acids by treatment with yellow ammonium sulfide. For example,  $\beta$ -acetophenone yields the amide of  $\beta$ -naphthylacetic acid, and  $\beta$ -propionaphthone yields the amide of  $\beta$ -( $\beta$ -naphthyl)-propionic acid.



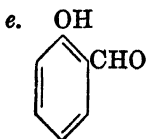
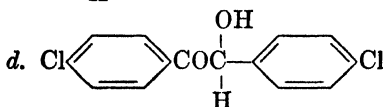
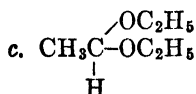
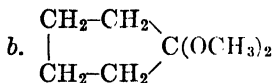


## PROBLEMS

1. By means of an equation indicate the reaction which takes place between



2. Outline a method for making



## SUGGESTED READINGS

ELDERFIELD, "A Review of Some Applications of the Cannizzaro Reaction to Aliphatic Aldehydes," *J. Chem. Education*, **7**, 594 (1930).

CORSON, "Aliphatic Acyloins. I. Preparation," *J. Am. Chem. Soc.*, **52**, 3988 (1930).

HANSLEY, "The Preparation of High Molecular Weight Acyloins," *J. Am. Chem. Soc.*, **57**, 2303 (1935).

BLATT, "The Beckmann Rearrangement," *Chem. Rev.*, **12**, 215 (1933).

LAUER and LANGKAMMERER, "The Constitution of the Bisulfite Addition Compounds of Aldehydes and Ketones," *J. Am. Chem. Soc.*, **57**, 2360 (1935).

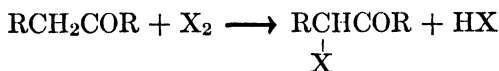
SHRINER and LAND, "The Structure of the Bisulfite Compound of Acetaldehyde," *J. Org. Chem.*, **6**, 888 (1941).

## CHAPTER XXIII

### SUBSTITUTION AND CONDENSATION REACTIONS OF CARBONYL COMPOUNDS

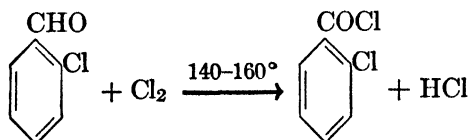
#### Halogenation

As has been mentioned earlier aldehydes and ketones which have an  $\alpha$ -hydrogen atom are readily halogenated by chlorine or bromine.

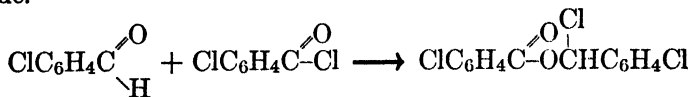


As a rule, esters cannot be halogenated successfully.

It is possible to convert an aldehyde into the corresponding acid chloride by direct chlorination. *o*-Chlorobenzoyl chloride is made in this way.



If the process is interrupted when half the theoretical amount of chlorine has been added and the reaction mixture is allowed to cool, a solid is formed which is an addition compound of the aldehyde with the acid chloride.



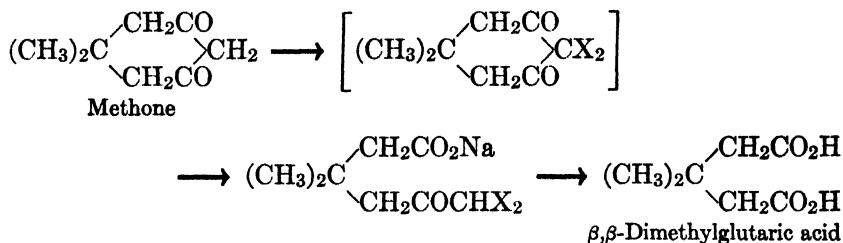
This reaction between an aldehyde and an acid chloride to give a chloro ester is general.

**The Haloform Reaction.** A reaction which is characteristic of methyl ketones is that brought about by the action of hypohalites. It converts methyl ketones to the salts of the corresponding acids (p. 81).



Alcohols whose oxidation products are methyl ketones give this reaction also. Ethyl alcohol and acetaldehyde give it but methanol does not.

$\beta$ -Diketones may also yield haloforms. The process probably involves cleavage of the dihalogen derivative. An interesting example is the degradation of methone to  $\beta,\beta$ -dimethylglutaric acid.



Perhaps the most elegant use of the haloform degradation is the conversion of unsaturated ketones to the corresponding acids. Ordinary oxidizing agents would attack the ethylenic bond. Cinnamic acid can be made from benzalacetone by this method.

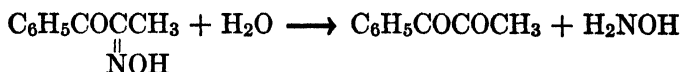
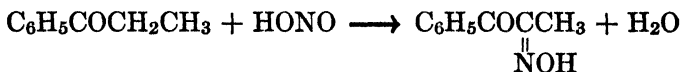


### Oxidation

Aldehydes and ketones which have a methylene group next to the carbonyl group are oxidized to dicarbonyl compounds by selenium dioxide.



The same transformation may be brought about by the use of nitrous acid. A ketoxime is formed and yields a dicarbonyl compound when hydrolyzed. The synthesis of methyl phenyl diketone is an example.

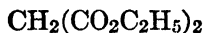


### Enolization

Enolization is characteristic of compounds which contain methylene, or methinyl groups situated between two carbonyl or similar unsaturated groups. Such groups exhibit unusual chemical reactivity, and are said to be "active." Malonic esters, acetoacetic esters, cyanoacetic esters, and 1,3-diketones such as acetylacetone and dibenzoylmethane are among the important examples.



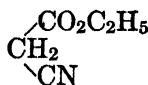
Acetoacetic ester



Malonic ester



Dibenzoylmethane



Cyanoacetic ester



Acetylacetone

The most important of these are ethyl acetoacetate and ethyl malonate, which have been considered earlier (p. 151). The properties of these substances will be set forth by reference to examples.

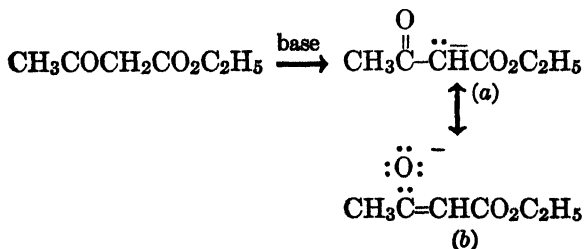
### Condensation Reactions

Aldehydes, ketones, esters, anhydrides, and similar compounds containing active hydrogen atoms undergo many reactions involving the formation of carbon-carbon linkages. Various types have been studied; among these are the aldol, Perkin, Knoevenagel, acetoacetic ester, Michael, Claisen, Claisen-Schmidt, Dieckmann, Tollens, and Mannich reactions. Actually many of these types of reactions are so similar that differentiation is often difficult.

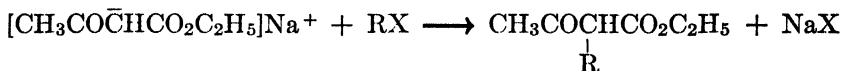
The most satisfactory classification which has been made separates these reactions into four categories: alkylation, the Claisen condensation, the aldol condensation, and the Michael condensation. The first three of these will be considered here: the Michael condensation will be discussed later (p. 337).

### Alkylation

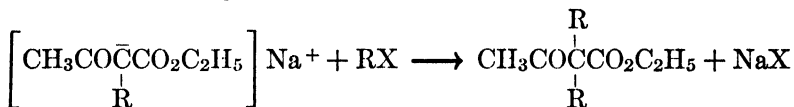
In the alkylation reaction (p. 151) the reactants are generally a reactive methylene compound, such as ethyl acetoacetate, and an alkyl halide. The reaction is usually effected by a base which presumably converts the active methylene compound into an enolate ion capable of acting as an electron donor. The alkylation of ethyl acetoacetate with *n*-butyl bromide may be used as an example.



The enolate ion is apparently a resonance hybrid of the structures *a* and *b*. It is alkylated by the alkyl halide. The reaction generally involves form *a*.

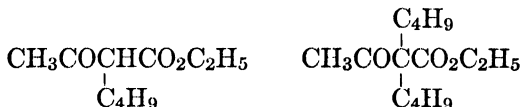


A second radical may be introduced if desired.

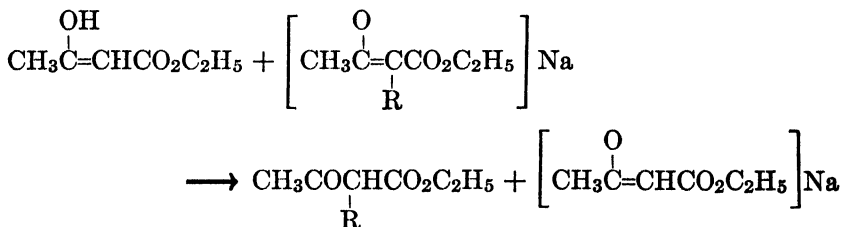


The two R groups so introduced may be alike or different. The introduction of the first alkyl radical greatly reduces the enolization tendency; this accounts for the fact that the second alkyl group tends to go in more slowly than the first.

With *n*-butyl bromide the following alkylation products are obtained:

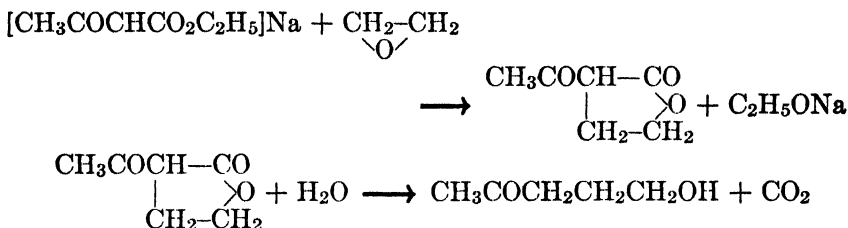


The enol form of the monoalkyl derivative is less acidic than that of the original ester. This is very fortunate because it permits the alkylation of the latter in the presence of the former, thus making possible monoalkylation with very little dialkylation. The explanation is to be sought in the ability of the more strongly acidic enol to compete successfully for the sodium.

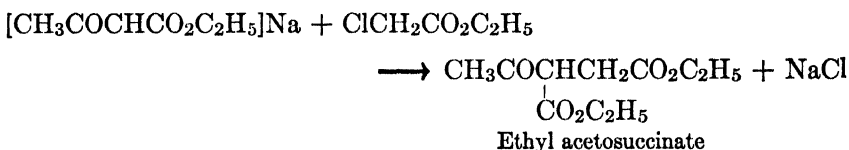


Primary and secondary alkyl halides give this reaction. Allyl and benzyl halides react very readily. Vinyl and aryl halides, however, do not react. Many other types of compounds react in the same way as do the alkyl halides. Acid chlorides and anhydrides give acylation products. Like other very reactive substances—such as  $\alpha$ -halogen ethers, for example—acid halides and anhydrides cannot be used in alcohol solution.

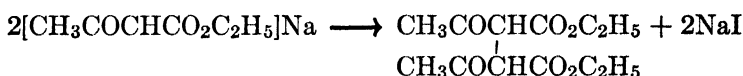
Ethylene oxide or ethylene chlorohydrin reacts to give a lactone. The latter can be transformed into acetopropyl alcohol.



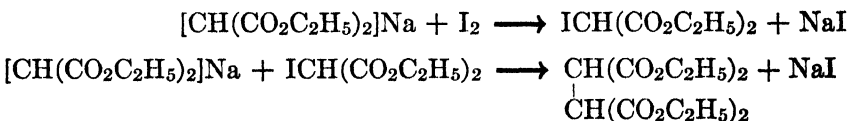
Ethyl acetosuccinate is made by condensing the sodium derivative of ethyl acetoacetate with ethyl chloroacetate.



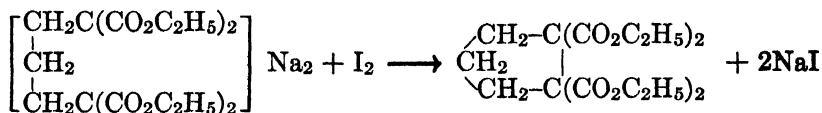
A reaction of especial interest takes place when the salt of ethyl acetoacetate or ethyl malonate is treated with iodine. Two molecules of ethyl acetoacetate are coupled together in the following manner:



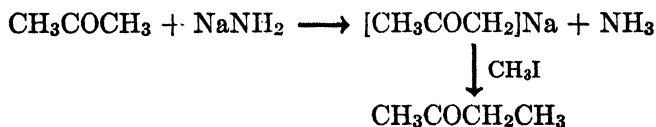
This is probably an alkylation involving the intermediate formation of an iodo ester which acts as the alkylating agent. Ethyl malonate may be used as an example.



This reaction has been used to form rings.

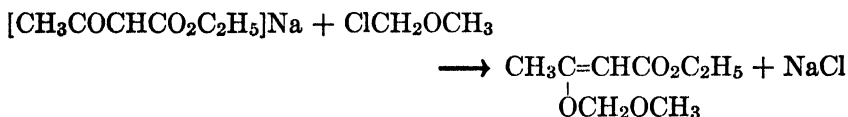


Ketones also may be alkylated. Sodium amide generally is used to form the enolate. From acetone methyl ethyl ketone may be made.



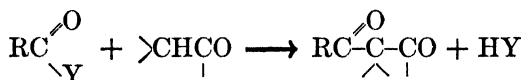
This process may be continued until six methyl groups have been introduced, forming hexamethylacetone,  $(\text{CH}_3)_3\text{CCOC}(\text{CH}_3)_3$ .

Chloromethyl ether is a very unusual alkylating agent, giving O-alkyl derivatives under ordinary conditions.

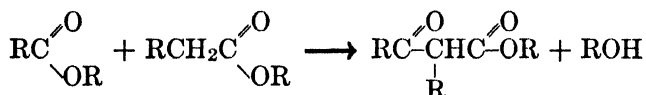


### The Claisen Condensation

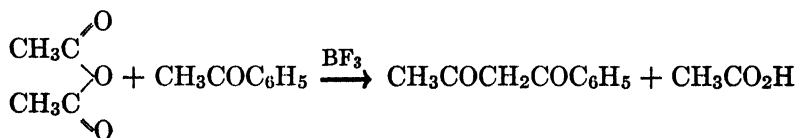
The Claisen type of condensation may be formulated as follows:



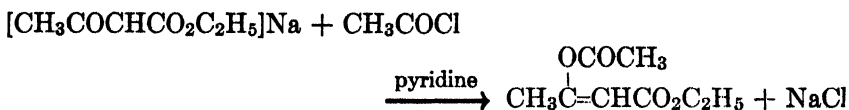
The electron-donating component is usually an ester or ketone and  $\text{RC}(\text{O})\text{Y}$  is generally an ester, anhydride, or acid chloride. The acetoacetic ester and Dieckmann condensations are to be regarded as special cases of the Claisen condensation.



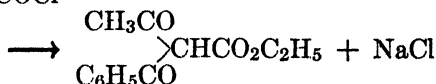
Whereas the Claisen condensation is usually effected by bases, an analogous reaction has been carried out between acetic anhydride and acetophenone with boron trifluoride as the catalyst.



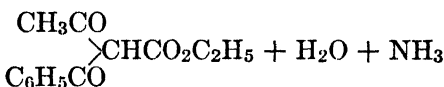
With active methylene compounds acid chlorides normally give C-acyl products but under certain special conditions O-acyl derivatives or enol esters may be produced. An example is the action of acetyl chloride on the sodium derivative of ethyl acetoacetate in the presence of pyridine.



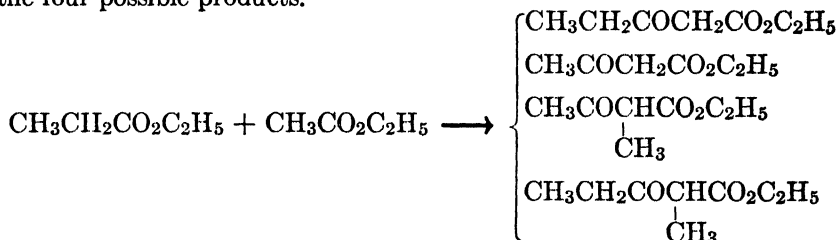
Benzoylation of ethyl acetoacetate leads to a diketo ester.



Hydrolysis with a very dilute solution of ammonia removes the acetyl group and serves as a preparative method for ethyl benzoylacetate.

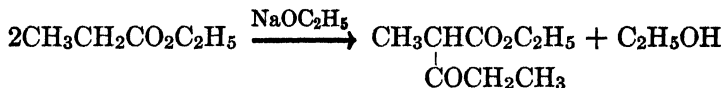


**Acetoacetic Ester Condensation.** The essential feature of the acetoacetic ester condensation is the elimination of the OR radical from one molecule of an ester along with an  $\alpha$ -hydrogen atom from another ester molecule. Mixtures of esters generally give mixtures of products. Thus ethyl acetate and ethyl propionate yield about equal amounts of the four possible products.

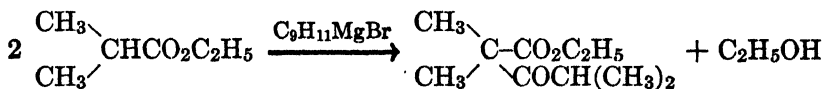


Exceptional in this respect is ethyl oxalate, which, having no  $\alpha$ -hydrogen atoms, cannot condense with itself in the Claisen manner.

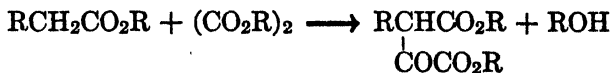
The acetoacetic ester reaction is very general but ordinarily does not occur unless the ester in question has two  $\alpha$ -hydrogen atoms. It is successful with ethyl propionate but fails with ethyl isobutyrate.



It has been found recently that even ethyl isobutyrate will condense in the presence of mesitylmagnesium bromide or sodium triphenylmethyl.

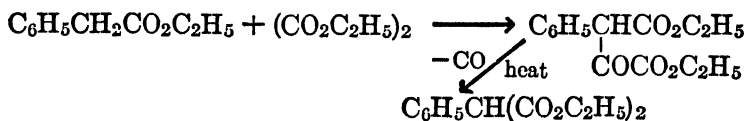


The condensation of ethyl oxalate with esters leads to the formation of  $\alpha$ -keto esters.

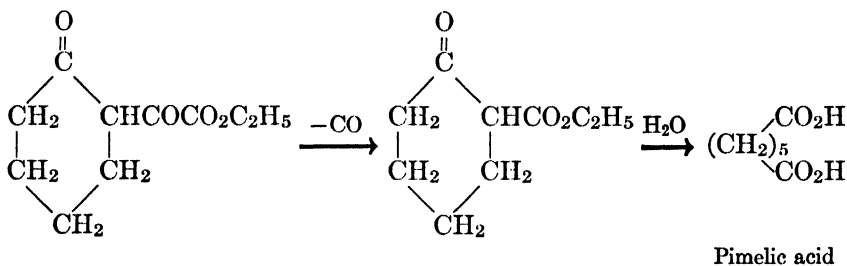




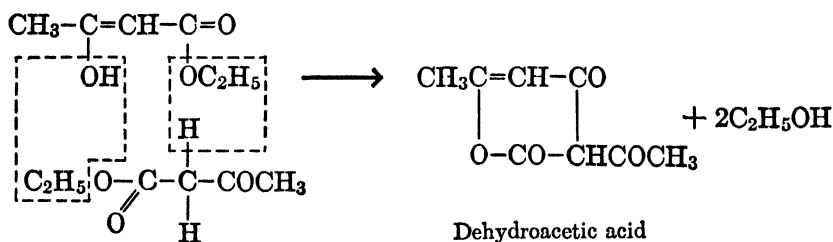
These have the remarkable property of decomposing thermally to give carbon monoxide and the corresponding substituted malonic ester. This reaction is used, for example, to make ethyl phenylmalonate.



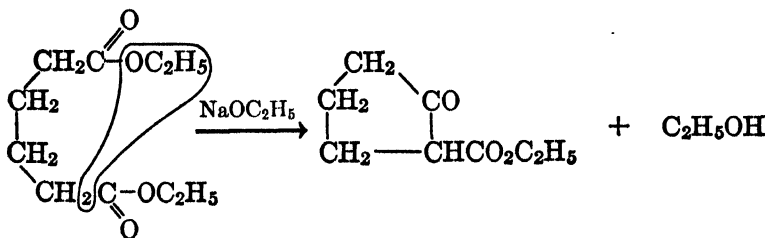
This type of transformation is also involved in the synthesis of pimelic acid from cyclohexanone. It consists in the hydrolysis of the keto ester obtained by pyrolysis of the ethoxalyl derivative.



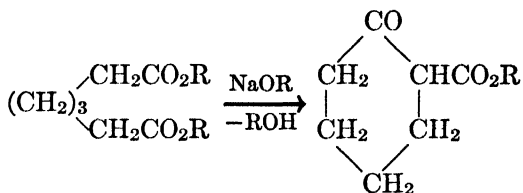
When heated alone ethyl acetoacetate yields dehydroacetic acid.



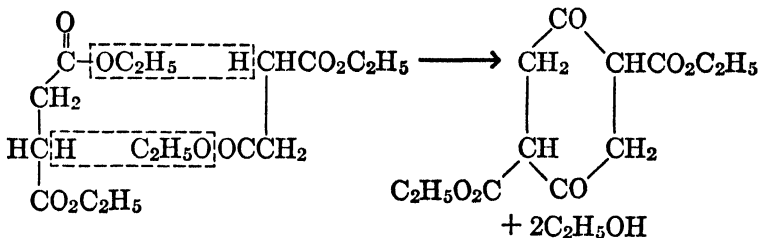
**Dieckmann Method.** When the Claisen condensation takes place intramolecularly it is generally spoken of as Dieckmann's method. For example, ethyl adipate reacts with sodium ethoxide to give 2-carbethoxycyclopentanone.



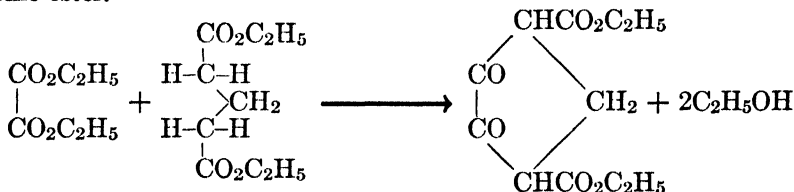
Pimelic esters react similarly to yield cyclohexanone derivatives after hydrolysis and decarboxylation of the cyclization product.



Many variations of this method have been discovered. Ethyl succinate, for example, gives succinosuccinic ester.

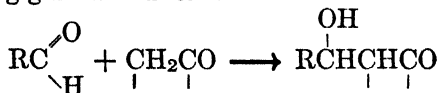


Ethyl oxalate can be condensed with ethyl glutarate to yield a diketonic ester.

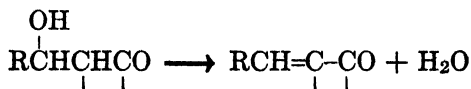


### The Aldol Condensation

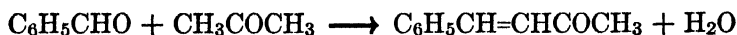
The aldol condensation embraces a group of reactions among which are the aldol, Perkin, Knoevenagel, Tollens, and Mannich condensations. The electron-accepting reactant is generally an aldehyde (but may be a ketone) and the electron-donating component may be an anhydride, ester,  $\beta$ -keto ester, or other active methylene compound. The reactions have the following generalized form:



Usually the  $\beta$ -hydroxy or aldol compound loses water.

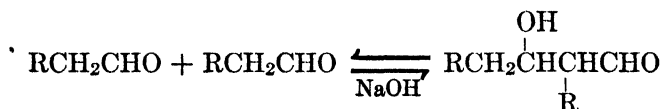


An example is the formation of benzalacetone from benzaldehyde and acetone.

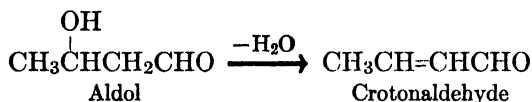


In the older classifications the term aldol condensation was reserved for the reaction between two molecules of a simple aldehyde or ketone. Less reactive substances require more drastic conditions and, by reference to these, various names have been given to the aldol type of reaction.

Aldehydes dimerize in the presence of alkalis to give aldols (p. 73).

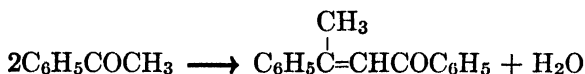


This type of reaction is very general. Usually the initial reaction product loses water, giving an  $\alpha,\beta$ -unsaturated carbonyl compound. Aldol itself, for example, is easily converted to crotonaldehyde (p. 74).



Aldol can be hydrogenated to give the corresponding glycol which when dehydrated yields 1,3-butadiene, a raw material for synthetic rubbers.

Acetophenone undergoes an analogous transformation under the influence of hydrogen chloride. The product is dypnone.



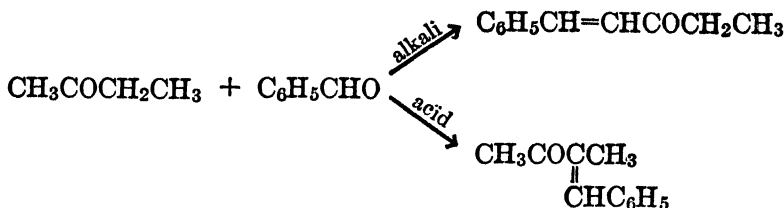
This condensation is best carried out with aluminum *t*-butoxide as the catalyst.

$\alpha,\beta$ -Unsaturated compounds in general tend to undergo chain cleavage under the influence of alkalis. This probably involves hydration to the aldol which then breaks down.

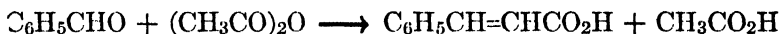


Methyl ethyl ketone is of exceptional interest because it can undergo aldol condensations involving either the methyl or the methylene group. It has been found experimentally that when the catalyst is hydrogen chloride the methylene group is attacked chiefly. Sodium ethoxide leads

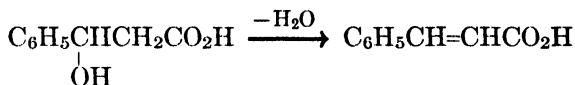
to condensations primarily affecting the methyl group. The condensation of methyl ethyl ketone with benzaldehyde illustrates this.



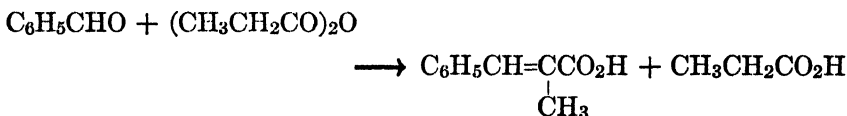
**Perkin Condensation.** Anhydrides are relatively unreactive and even with aldehydes require long treatment at elevated temperatures. These are the conditions which characterize the Perkin reaction. Thus benzaldehyde, when heated with a mixture of sodium acetate and acetic anhydride, gives rise to cinnamic acid.



This probably proceeds through the intermediate hydroxy acid.

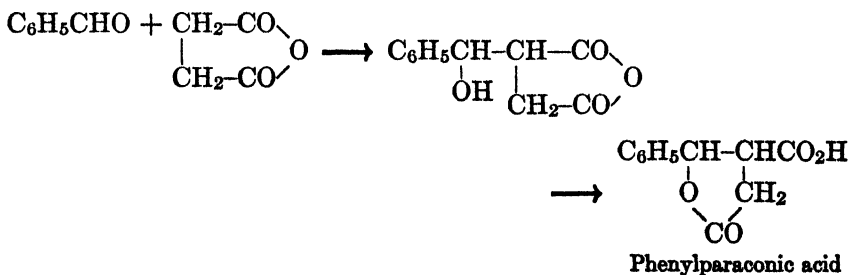


The reaction is general for aromatic aldehydes. Condensation always takes place on the  $\alpha$ -carbon atom of the reagent. Thus, from propionic anhydride and sodium propionate  $\alpha$ -methylcinnamic acid is produced.

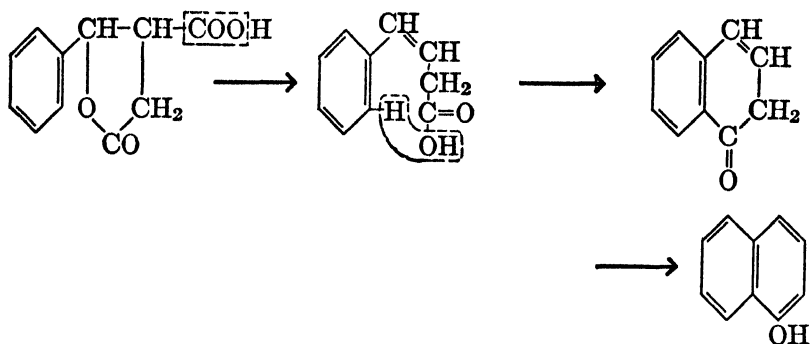


It is now generally accepted that the condensation takes place between the aldehyde and the anhydride, the salt merely acting as a catalyst.

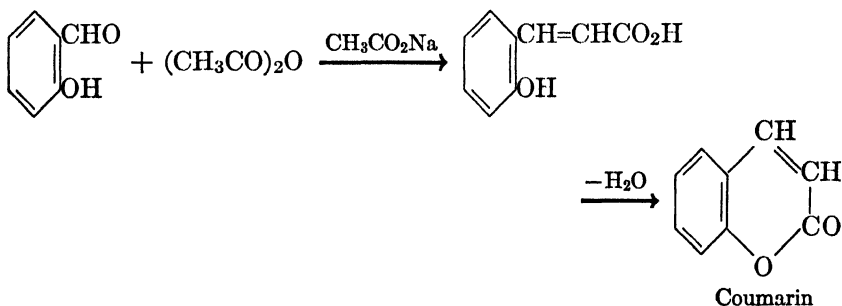
An interesting example of the Perkin reaction is the condensation between benzaldehyde, succinic anhydride, and sodium acetate.



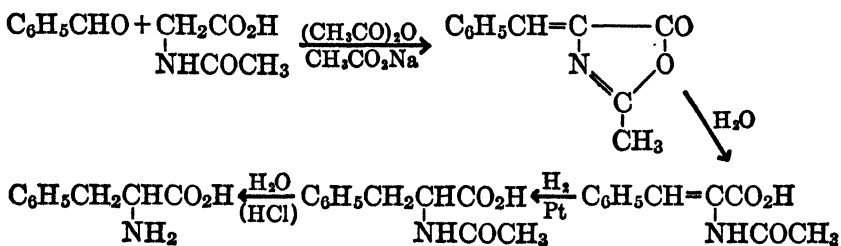
Apparently the aldol rearranges, for the final product is the lactonic acid, phenylparaconic acid. This acid is of particular interest because heat converts it to  $\alpha$ -naphthol.



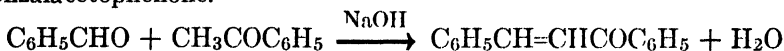
Applied to salicylaldehyde, the Perkin synthesis yields the salt of  $\alpha$ -hydroxycinnamic acid. The free acid, however, is unstable and immediately forms the lactone, coumarin.



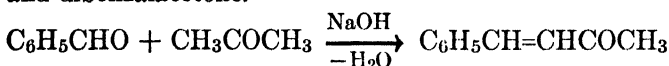
The Perkin condensation is also involved in the synthesis of amino acids through the azlactones. The method is illustrated by the preparation of *dl* phenylalanine from benzaldehyde and acetaminobenzoic acid. The product of the condensation, known as an azlactone, is converted to the amino acid by a series of transformations involving hydrolysis, hydrogenation, and a second hydrolysis.



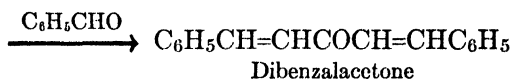
**Claisen-Schmidt Method.** Schmidt introduced the use of a 10 per cent aqueous sodium hydroxide solution as catalyst. By this method, for example, benzaldehyde is caused to react with acetophenone to give benzalacetophenone.



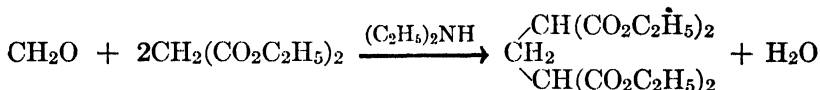
Similarly from benzaldehyde and acetone are obtained benzalacetone and dibenzalacetone.



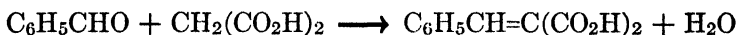
Benzalacetone



**Knoevenagel Method.** Knoevenagel found that condensations between carbonyl compounds and active methylene compounds often could be effected by using ammonia or an amine as the catalyst. Piperidine and diethylamine are probably used more frequently than other amines. An example is the condensation of formaldehyde with ethyl malonate.

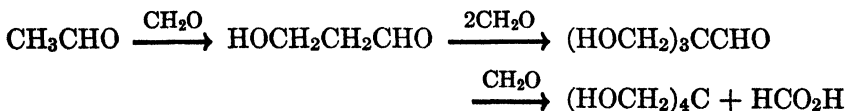


Similarly benzaldehyde condenses with malonic acid in the presence of piperidine.



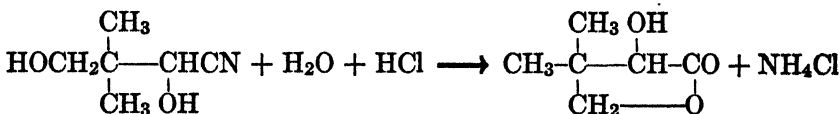
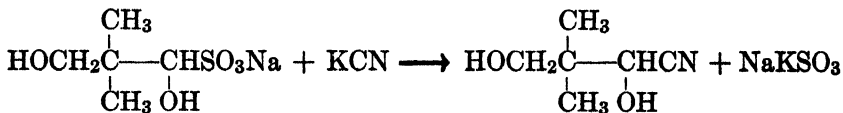
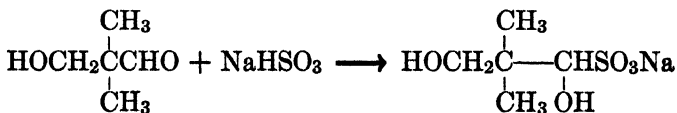
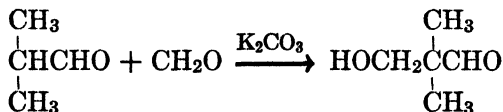
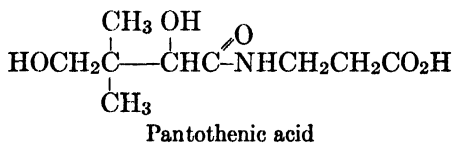
It has recently been shown that the catalyst in the Knoevenagel reaction is really the ammonium (piperidinium, diethylammonium) ion formed by traces of acid present in the aldehyde. If the aldehyde is freed from acid the reaction does not take place. Unless one of the reactants is an acid, it is best to use piperidine acetate.

**Tollens' Condensation.** Tollens developed a method of condensing formaldehyde with aldehydes and ketones which depends on the use of calcium hydroxide as catalyst. It requires long treatment and tends to give polymethylol derivatives. An interesting example is the synthesis of pentaerythritol from acetaldehyde.



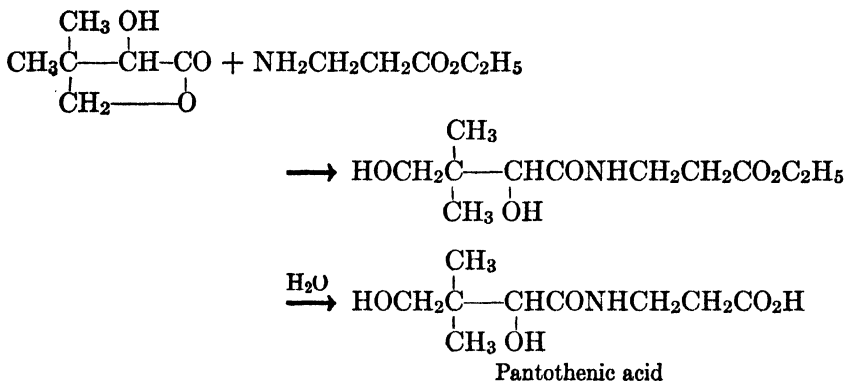
It will be noted that the process involves a threefold aldol condensation followed by a "crossed" Cannizzaro reaction.

The synthesis of pantothenic acid involves an interesting example of the Tollens condensation. Pantothenic acid, a member of the vitamin B group, has been found in a great variety of foods. It has growth-promoting properties and a curative action against dermatitis developing in chicks fed on a heated diet. Pantothenic acid consists of (+) $\alpha,\gamma$ -dihydroxy- $\beta,\beta$ -dimethylbutyric acid joined with  $\beta$ -aminopropionic acid ( $\beta$ -alanine) by means of an amide linkage.



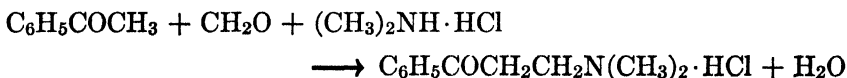
The dihydroxy acid was resolved by means of its quinine salt and the active lactones were condensed with  $\beta$ -alanine ester to give the two

ethyl pantothenates. Hydrolysis of these yielded (+) rotatory and (-) rotatory pantothenic acids.



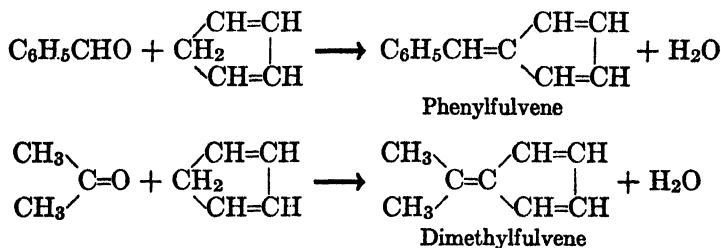
The synthetic (+) pantothenic acid showed the expected biological activity when assayed on chicks and rats.

**Mannich Reaction.** If aldol condensations are carried out in the presence of amines, amino ketones frequently result. The interaction of formaldehyde, acetophenone, and dimethylamine is an example. In practice the base is isolated as the hydrochloride.



This is known as the Mannich reaction.

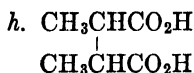
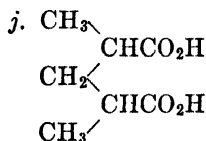
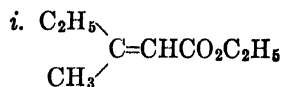
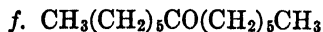
**Reactions of Hydrocarbons Which Contain Active Methylene Groups.** Especial mention must be made of certain active methylene compounds which bear no formal resemblance to carbonyl compounds. These are cyclopentadiene and its benzologs, indene and fluorene. They enter into condensation reactions with aldehydes and ketones to give fulvenes. Cyclopentadiene reacts with benzaldehyde and acetone to give phenyl- and dimethylfulvene, respectively.



It is interesting to note that dimethylfulvene possesses active hydrogen—a fact which is in harmony with its vinylogous relationship to cyclo-







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FUSON and BULL, "The Haloform Reaction," *Chem. Rev.*, **15**, 275 (1934).

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MEERWEIN and VASSEN, "Synthesen von Ketonen und  $\beta$ -Diketonen mit Hilfe von Borfluorid," *J. prakt. Chem.*, **141**, 149 (1934).

ADAMS and VOLWILER, "The Reaction Between Acid Halides and Aldehydes," *J. Am. Chem. Soc.*, **40**, 1732 (1918).

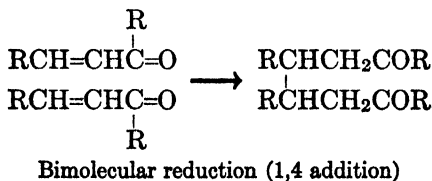
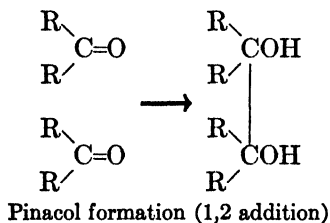
## CHAPTER XXIV

### UNSATURATED CARBONYL COMPOUNDS

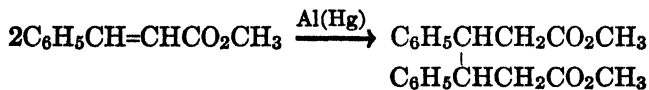
Unsaturated carbonyl compounds result from many of the condensations considered in the preceding chapter and are known in large numbers and in great variety. In general they possess the properties of olefins as well as those of saturated carbonyl compounds. However, if the ethylenic bond is in the  $\alpha, \beta$  position with respect to the carbonyl group, i.e., if the two form a conjugated system, certain peculiarities are encountered.

The addition of Grignard reagents in the 1,4 manner already has been mentioned. Actually, 1,4 addition of a Grignard reagent to an aldehyde has been observed rarely. Many ketones and esters, however, react in this way.

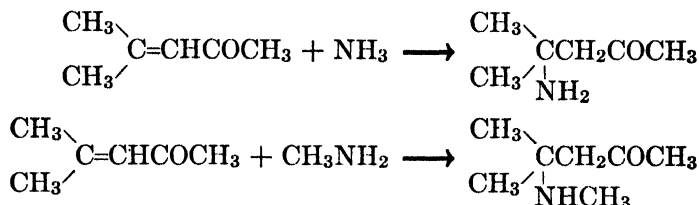
**Bimolecular Reduction.**  $\alpha, \beta$ -Unsaturated ketones and esters often undergo bimolecular reduction in which the two simple molecules are joined not at position 2 but at position 4. This may be thought of as 1,4 addition as contrasted to pinacol formation which is to be regarded as 1,2 addition.



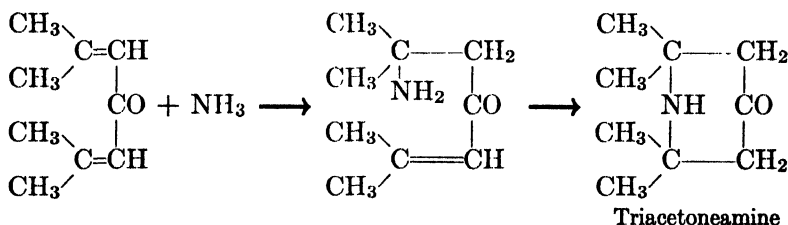
An example of bimolecular reduction of this type is the conversion of methyl cinnamate to methyl  $\beta, \beta'$ -diphenyladipate.



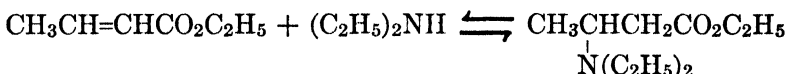
**Ammonia and Amines.**  $\alpha,\beta$ -Unsaturated ketones and esters react with ammonia and primary and secondary amines to give  $\beta$ -amino compounds. Mesityl oxide, for example, combines with ammonia and with methylamine as follows:



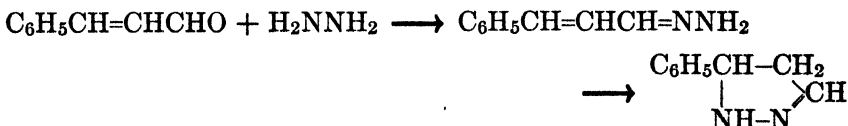
Phorone condenses with ammonia to form triacetoneamine. The mechanism appears to involve two steps each of which may be looked upon as being of the 1,4 type.



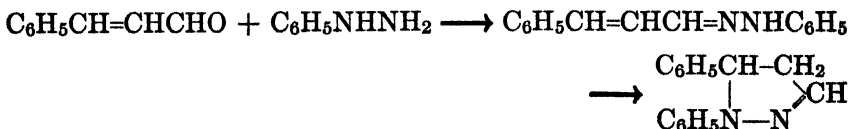
Ethyl crotonate combines with diethylamine to give the corresponding  $\beta$ -amino propionate. The reaction can be reversed by heat.



**Hydrazine.** The reaction between aldehydes and hydrazines normally leads to the formation of azines. However, unsaturated aldehydes tend to undergo ring closure to give pyrazolines. Cinnamaldehyde reacts in this manner when treated with an excess of hydrazine; the product is 5-phenylpyrazoline.

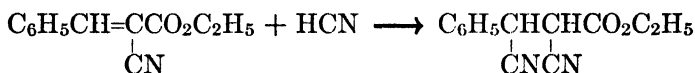
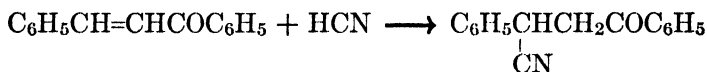


Phenylhydrazine reacts similarly to give 1,5-diphenylpyrazoline.

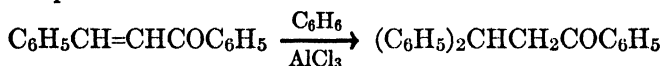


The ring closure in these examples is due to an addition of the 1,4 type.

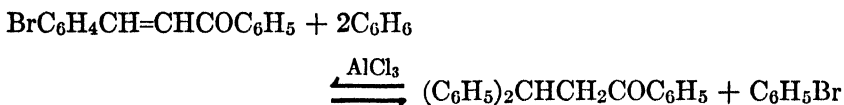
**Hydrogen Cyanide.** Whereas the formation of cyanohydrins by the addition of hydrogen cyanide is limited to aldehydes and a few of the more reactive ketones, 1,4 addition will occur with many ketones and esters. Benzalacetophenone and ethyl  $\alpha$ -cyanocinnamate undergo this type of reaction.



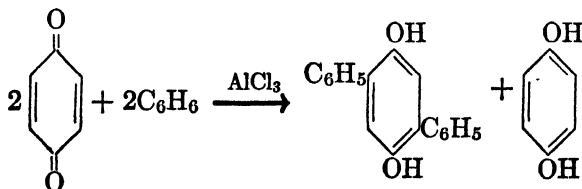
**Aromatic Hydrocarbons.** It has been pointed out that aromatic hydrocarbons may combine with olefinic compounds in the presence of aluminum chloride. If the olefinic bond is conjugated with a carbonyl group the addition is still possible but always produces a  $\beta$ -aryl derivative. It probably should be classified as of the 1,4 category. This reaction will not occur unless hydrogen chloride is present, and it seems likely that 1,4 addition of the hydrogen halide is the first step. The second step would then be a normal alkylation. Many condensations of this type are known. An interesting example is the addition of benzene to benzalacetophenone.



This reaction appears to take place reversibly, for, in benzene solution, *p*-bromobenzalacetophenone gives the same product; bromobenzene is also formed.

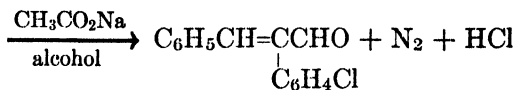


Cinnamic acid and *p*-benzoquinone also react. From the latter 2,5-diphenylhydroquinone is formed.



However, a method is known by which  $\alpha,\beta$ -unsaturated carbonyl compounds can be arylated in the  $\alpha$ -position. This consists in treating

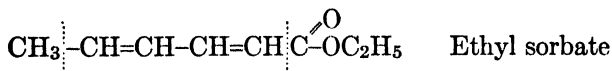
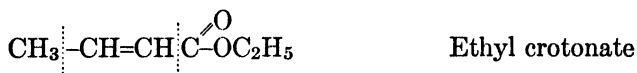
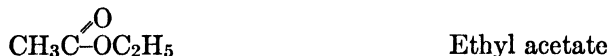
the unsaturated compound with an aryldiazonium chloride or bromide.  $\alpha$ -(*p*-Chlorophenyl)-cinnamaldehyde can be made in this way.



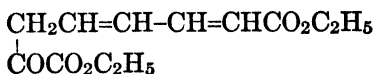
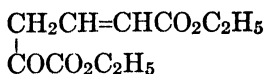
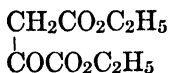
### The Principle of Vinylogy

This principle is an empirical rule formulated so as to include as many as possible of the peculiar effects ordinarily ascribed to conjugation. With reference to a conjugated system of the type  $\text{R}-(\text{C}=\text{C})_n-\underset{2}{\text{C}}=\underset{1}{\text{C}}=\text{O}$ , the principle states that the function of the oxygen atom does not change with  $n$ , and that the function of carbon atom 2 may be usurped by the carbon atom joined to R.

An interesting example of the operation of this principle is furnished by the vinylogous series ethyl acetate, ethyl crotonate, and ethyl sorbate.



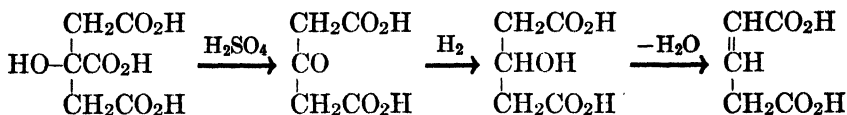
In each the terminal methyl group is reactive. With ethyl oxalate in the presence of potassium ethoxide they give the corresponding ethyl oxalyl derivatives.



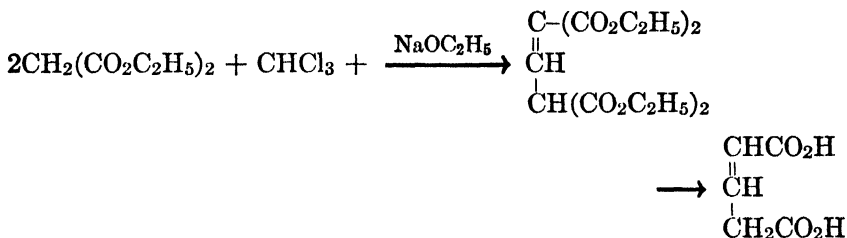
### Glutaconic Esters

Another conspicuous example of the vinylogy principle is found in a comparison of malonic ester with its next higher vinylog, glutaconic

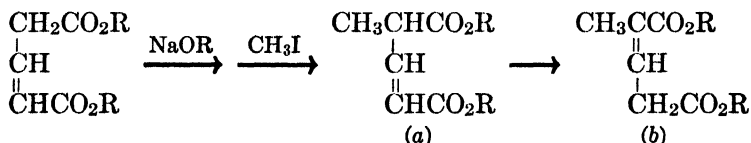
ester. Glutaconic acid is made from citric acid by the following series of transformations:



It can also be made from malonic ester and chloroform.

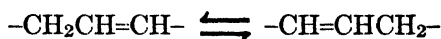


The methylene group exhibits an activity similar to that in malonic esters. Glutaconic esters can be alkylated, for example.

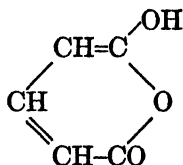


The monomethyl compound (a) rearranges to an isomeric form (b) by a shift of a hydrogen atom, and the second methyl group goes on the new methylene group to give the  $\alpha, \alpha'$ -dimethyl derivative.

The ready rearrangement of glutaconic acid and its derivatives is due to the mobile three-carbon system.



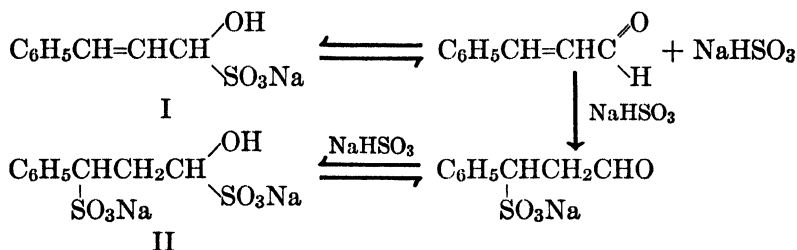
Of especial interest is the anhydride, which exists as an enol.



### Unsaturated Aldehydes

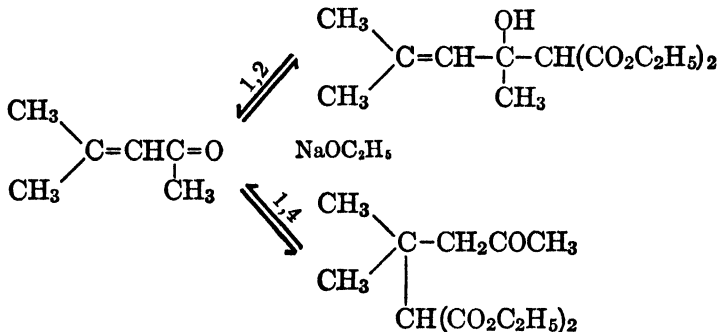
An interesting example of 1,4 addition is observed when cinnamaldehyde is treated with sodium bisulfite. Addition takes place reversibly in the 1,2 manner, and irreversibly and much more slowly in the 1,4

manner. The primary addition product (I) if allowed to stand in solution gradually changes to the di-bisulfite addition product (II) with the liberation of an equivalent amount of free aldehyde.

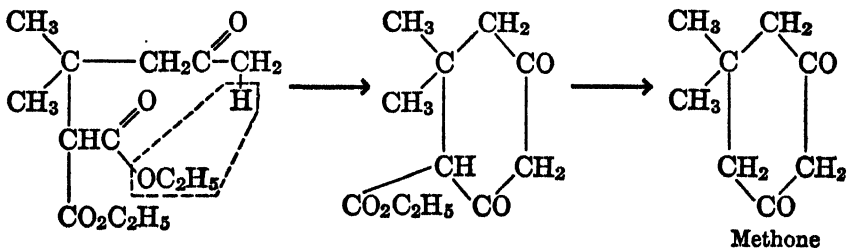


### Michael Condensation

Active methylene compounds have been found to react in the 1,4 manner with many  $\alpha,\beta$ -unsaturated ketones and esters. This is known as the Michael condensation. The condensation of malonic ester with mesityl oxide is an example. Here we might expect 1,2 (aldol) condensation or 1,4 (Michael) condensation.

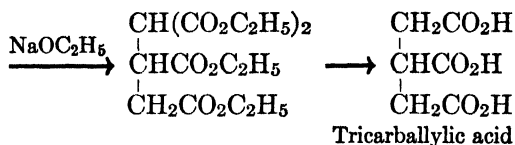


It is to be emphasized that, like the aldol condensation, the Michael condensation is reversible. In the above case the Michael is the one actually observed. Subsequent transformations of the product yield methone.

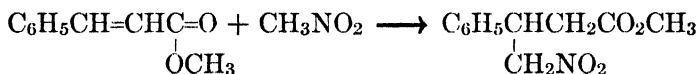




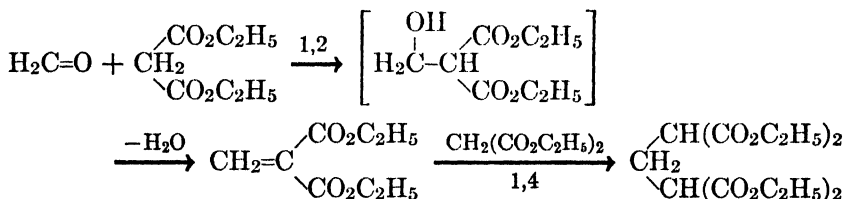
Another example of the use of the Michael reaction is the synthesis of tricarballic acid from ethyl fumarate and malonic ester.



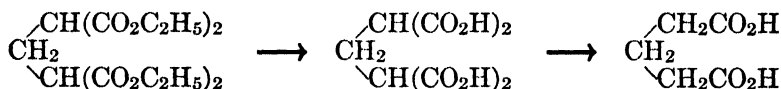
The Michael condensation is widely applicable. Nitromethane, for example, reacts with methyl cinnamate in the 1,4 manner.



The condensation of two molecules of ethyl malonate with one of formaldehyde (p. 327) appears to involve 1,2 or aldol addition followed by 1,4 or Michael addition.



Hydrolysis of the complex ester and decarboxylation of the corresponding acid yield glutaric acid.

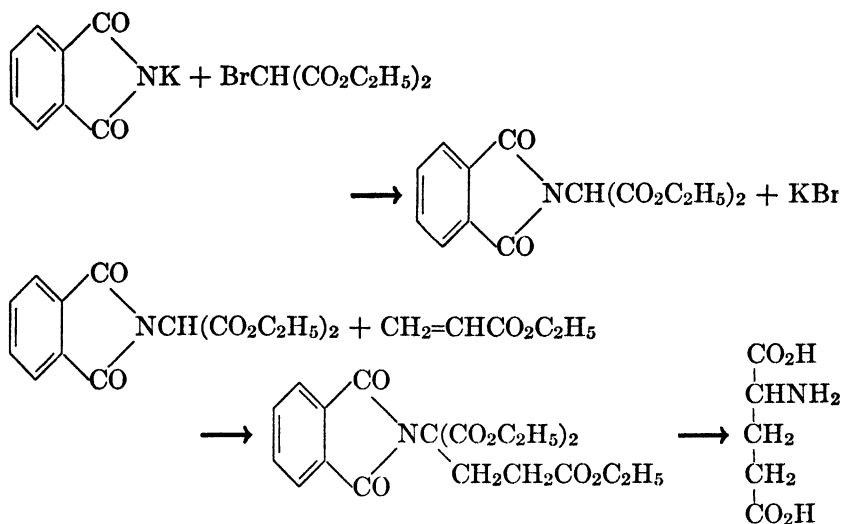


The same sequence of condensation reactions is encountered in the reaction of benzaldehyde with acetophenone. At temperatures below 30°, benzalacetophenone—the result of 1,2 addition—is the principal product. At higher temperatures 1,4 addition of acetophenone to benzalacetophenone occurs.

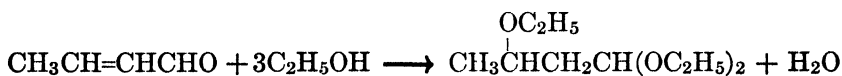


From this example it is seen that saturated ketones are sufficiently reactive to enter into Michael condensations.

The synthesis of *dl* glutamic acid from ethyl bromomalonate, phthalimide, and ethyl acrylate illustrates the use of the Michael condensation in conjunction with Gabriel's amine synthesis (p. 388).

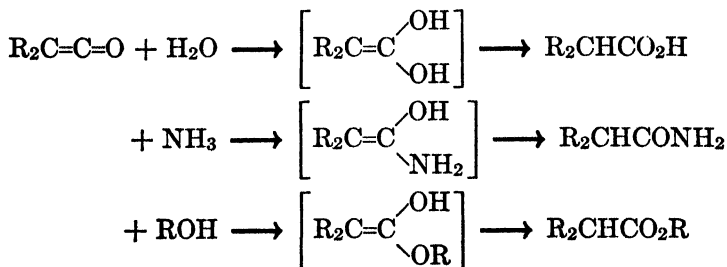


**Acetalization.** Acetalization of  $\alpha,\beta$ -unsaturated aldehydes is complicated by addition to the conjugated system. The product is the  $\beta$ -alkoxy acetal formed by addition of a molecule of alcohol to the aldehyde and subsequent transformation into the acetal. Crotonaldehyde with ethyl alcohol gives  $\beta$ -ethoxy-*n*-butyraldehyde acetal.

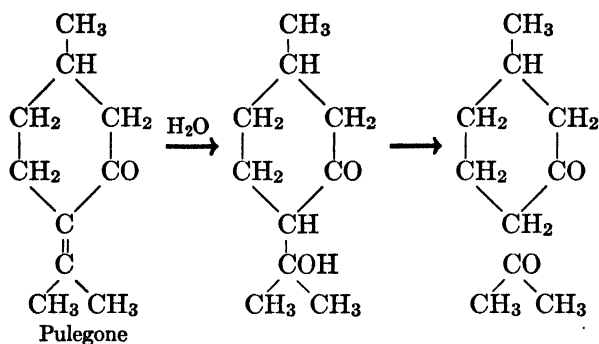


A way around the difficulty is illustrated in the synthesis of glyceraldehyde given on p. 302.

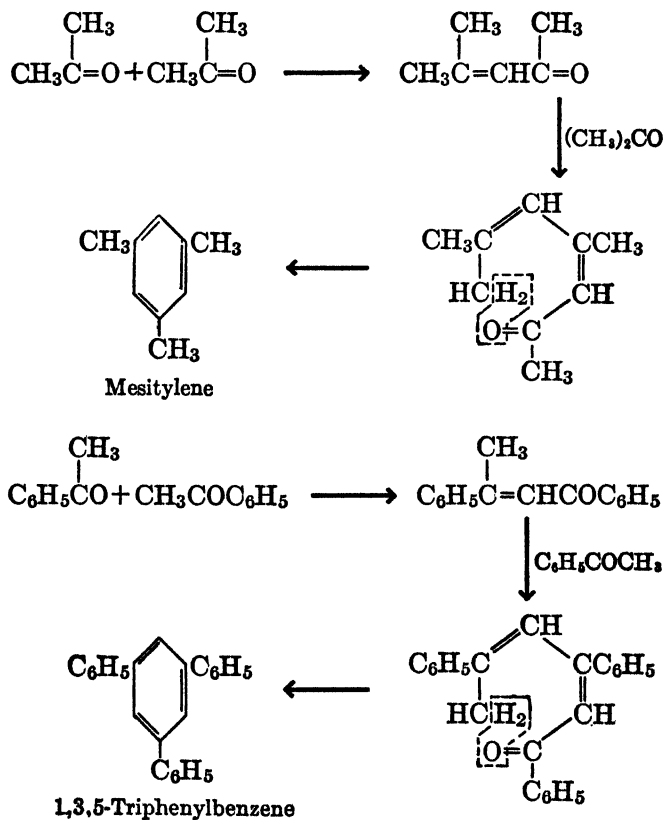
**Ketenes.** Ketenes are unsaturated ketones in which an olefinic double bond is twinned with the carbonyl double bond. They may be looked upon as intramolecular anhydrides. Actually their reactions are generally those of acid anhydrides. It is believed that a ketene reacts as a typical carbonyl compound; in most instances the initial addition compound is unstable and rearranges. The reactions with water, ammonia, and alcohols are illustrative.







**1,3,5-Trisubstituted Benzenes.** The processes leading to the formation of mesitylene and 1,3,5-triphenylbenzene from acetone and acetophenone, respectively, can be formulated as follows. It will be noted that the last step in each case is a condensation involving an active methyl group joined to a carbonyl group by a system of two vinylenes linkages.



## SUGGESTED READINGS

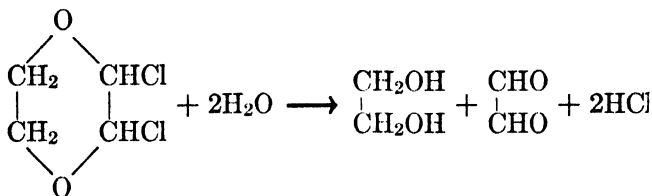
- ALLEN and BLATT, "Unsaturation and Conjugation," Gilman's *Organic Chemistry*, Chapter 6. John Wiley and Sons, New York, 1938.
- FUSON, "The Principle of Vinylogy," *Chem. Rev.*, **16**, 1 (1935).
- TAYLOR and CONNOR, "Michael Condensation. VII. Activation of the Methylene Group by Carbon-Carbon Unsaturation," *J. Org. Chem.*, **6**, 696 (1941).

## CHAPTER XXV

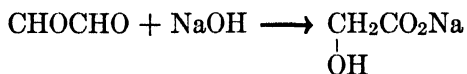
### COMPOUNDS WHICH CONTAIN TWO OR MORE CARBONYL GROUPS

#### Dialdehydes

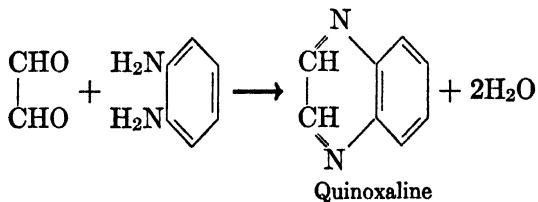
Glyoxal, the simplest dialdehyde, is made in 40 per cent yield by the oxidation of acetaldehyde by selenium dioxide. When glyoxal is needed as an intermediate it may be made by hydrolysis of dichlorodioxane.



Monomeric glyoxal is a green gas under ordinary conditions, and is the simplest colored organic molecule. Like other glyoxals it is transformed by alkalis into the salt of the corresponding hydroxy acid.



It reacts with *o*-phenylenediamine to give quinoxaline.



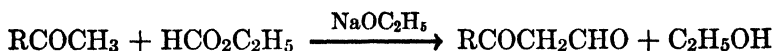
This reaction is characteristic of compounds which contain "twinned" carbonyl groups,  $-\text{COCO}-$ .

#### Ketoaldehydes

Glyoxals have the general formula  $\text{RCOCHO}$  and are  $\alpha$ -ketoaldehydes. They resemble glyoxal itself but are generally more stable. However, all show a great tendency to polymerize.

**$\beta$ -Ketoaldehydes**

$\beta$ -Ketoaldehydes are interesting because they exist only in the enolic modification. They can be made by the Claisen condensation between ketones and ethyl formate.



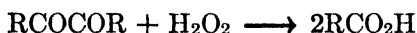
Evidently the aldehydic form changes to the enol form.



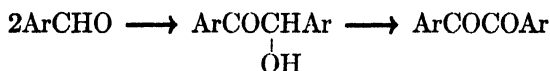
For this reason the substances are called "hydroxymethylene" compounds. These compounds are among the few which violate Erlenmeyer's rule that the grouping  $\begin{array}{c} | \\ \text{C}=\text{C}-\text{OH} \\ | \end{array}$  is incapable of existence.

**Diketones**

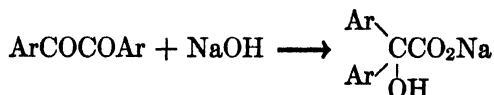
$\alpha$ -Diketones such as biacetyl are distinguished from other types of diketones by their ability to form quinoxalines and by the fact that they are cleaved by hydrogen peroxide.



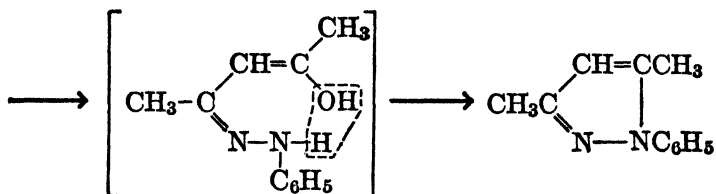
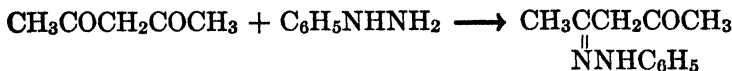
In the aromatic series benzils are made by oxidation of benzoinz formed by condensation of aldehydes.



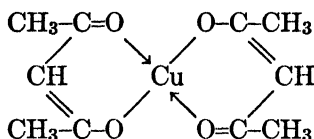
Benzils rearrange to salts of benzilic acids when heated with alkalis.



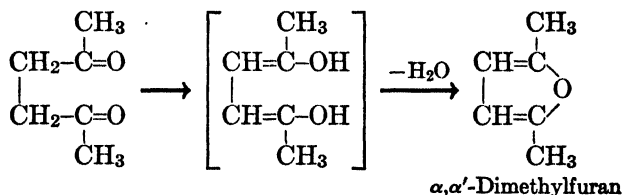
$\beta$ -Diketones such as acetylacetone have an active methylene group and show properties typical of active methylene compounds.  $\beta$ -Diketones react with phenylhydrazine to give phenylhydrazones which, however, are unstable and form cyclic compounds by loss of water. These heterocyclic derivatives are known as pyrazoles. Acetylacetone yields 1-phenyl-3,5-dimethylpyrazole.



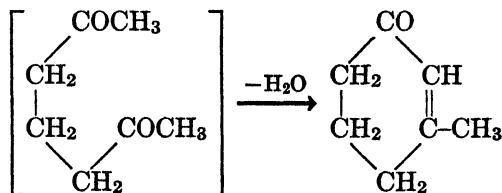
$\beta$ -Diketones also are peculiar in that they form chelated metal salts. The copper salt of acetylacetone, for example, has the following structure:



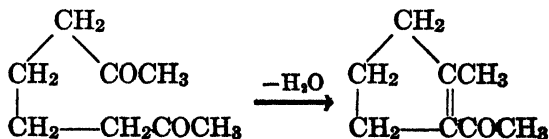
$\gamma$ -Diketones show a great tendency to yield furans. If acetylacetone is treated with a dehydrating agent  $\alpha,\alpha'$ -dimethylfuran is formed. Presumably the enol form is an intermediate.



$\delta$ -Diketones undergo cyclization so readily that they cannot be isolated; cyclohexenones are obtained instead.

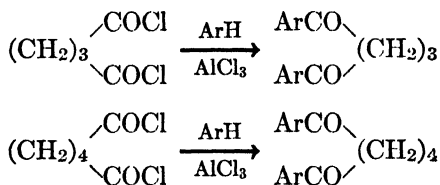


α-Diketones cyclize readily but can be obtained as such. The ring closure gives a cyclopentene derivative.



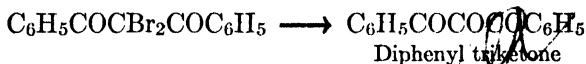


Aromatic  $\delta$ - and  $\epsilon$ -diketones are made by the Friedel-Crafts reaction and are stable.

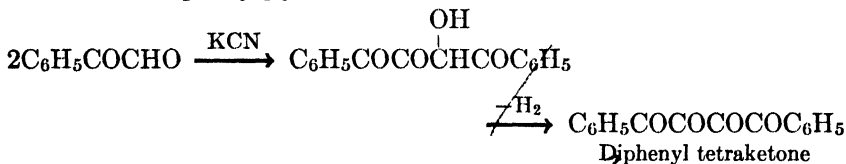


### Polycarbonyl Compounds

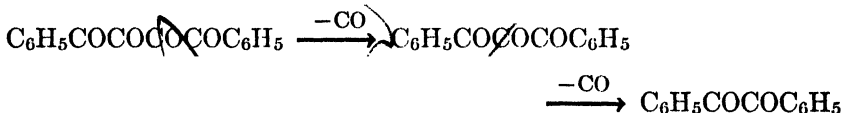
Triketones and tetraketones are also known. Diphenyl triketone, for example, is a yellow solid resulting from the hydrolysis of dibromodibenzoylmethane.



The corresponding tetraketone can be made by oxidation of the formoin obtained from phenylglyoxal.



Both the tri- and tetraketones tend to lose carbon monoxide to form the next lower member of the series.

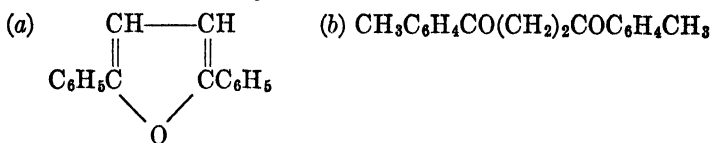


This reaction is reminiscent of that of ethyl oxalyl derivatives of esters; it is catalyzed by cupric salts.

### PROBLEMS

- What is the action of hot aqueous alkali on  
 (a)  $\text{C}_6\text{H}_5\text{CHO}$ ? (b)  $\text{C}_6\text{H}_5\text{COCHO}$ ? (c)  $\text{C}_6\text{H}_5\text{COCH}_3$ ?
- Suggest ways of distinguishing between  
 (a)  $\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5$  and  $\text{C}_6\text{H}_5\text{COCH}_2\text{COC}_6\text{H}_5$   
 (b)  $\text{CH}_3\text{COCOC}_6\text{H}_5$  and  $\text{CH}_3\text{CH}_2\text{COCHO}$   
 (c)  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COCH}_3$  and  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{COCH}_3$

3. Indicate a method of synthesis for



## SUGGESTED READING

STEIN, "Oxidations with Selenium Dioxide," *Angew. Chem.*, **54**, 77-85 (1941).

# CHAPTER XXVI

## RING FORMATION

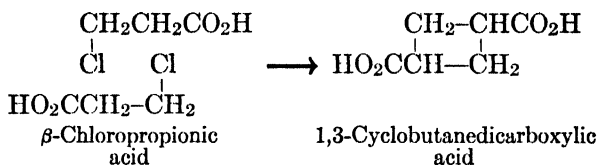
### Historical

A compound which contains two functional groups capable of reacting with each other may react with itself either to give a *ring compound* or a *polymer*. Which of these will happen appears to depend chiefly on the size of the ring to be formed. It was early observed that six-membered rings formed easily, whereas rings of other sizes were unknown in nature and had not been synthesized. Indeed, until about the year 1880 it was generally supposed that rings smaller or larger than this could not exist. Moreover, there were theoretical grounds for this opinion, for it was evident that the three- and four-membered rings, at least, could not be made from carbon atoms having the rigid tetrahedral form which had been used so successfully in solving structural problems. If the four bonds of a carbon atom are directed towards the vertices of a regular tetrahedron, each forms an angle of 109 degrees 28 minutes with the others. As a matter of fact, it is impossible by use of such atoms to construct any ring of fewer than five members. The following table shows the angles which are required for the formation of the smaller rings together with the deviation in each of the valence bonds from the normal position in the regular tetrahedron.

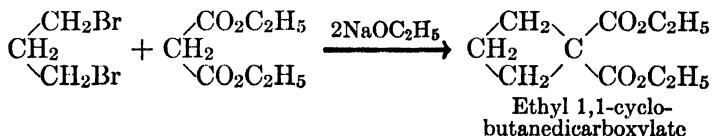
TABLE XXXI  
VALENCE ANGLES AND DEVIATIONS

Hydrocarbon	Formula	Angle	Deviation
Ethylene (cycloethane)	$\text{CH}_2=\text{CH}_2$	$0^\circ$	$54^\circ 44'$
Cyclopropane	$\begin{array}{c} \text{CH}_2-\text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}_2 \end{array}$	$60^\circ$	$24^\circ 44'$
Cyclobutane	$\begin{array}{cc} \text{CH}_2-\text{CH}_2 & \\   &   \\ \text{CH}_2-\text{CH}_2 & \end{array}$	$90^\circ$	$9^\circ 44'$
Cyclopentane	$\begin{array}{ccc} \text{CH}_2-\text{CH}_2 & & \text{CH}_2 \\   & \diagdown & / \\ \text{CH}_2-\text{CH}_2 & & \end{array}$	$108^\circ$	$0^\circ 44'$

Between 1880 and 1885, however, came a rapid succession of events which revolutionized chemists' ideas of ring compounds and laid the foundations of modern alicyclic chemistry. The first of these was the discovery that  $\beta$ -chloropropionic acid when heated with dry sodium ethoxide was converted to a compound containing a ring of four carbon atoms—1,3-cyclobutanedicarboxylic acid.



Almost immediately after this, Freund succeeded in making cyclopropane—a hydrocarbon containing a three-membered ring—by the action of sodium on trimethylene bromide. A little later Perkin found that ethyl malonate condenses with trimethylene bromide in the presence of sodium ethoxide to give ethyl 1,1-cyclobutanedicarboxylate.



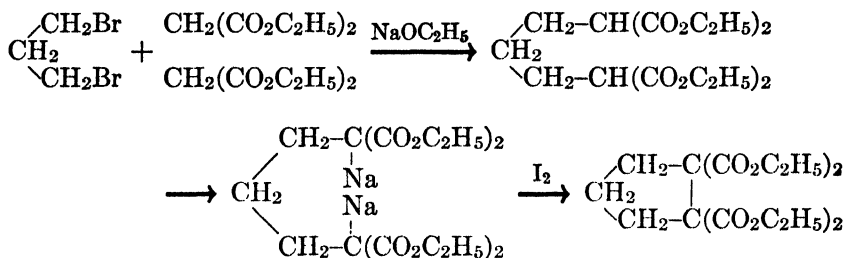
These results established the existence of three- and four-membered carbon rings and demanded drastic revision of the current opinions regarding the stereochemical character of the carbon atom.

### The Baeyer Strain Theory

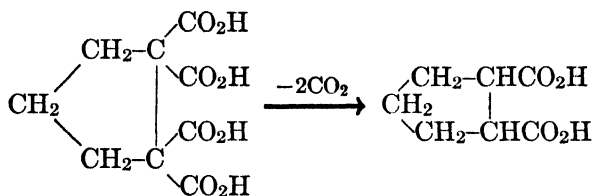
An ingenious and very plausible solution to the problem was advanced by Baeyer, who assumed that the normal angle between the valence bonds of carbon was 109 degrees 28 minutes, but *that it was possible for this angle to be altered*. Any deviation from this angle was, however, supposed to bring about a condition of *strain* which was, according to the theory, attended by a corresponding decrease in stability. The greater the strain involved the less would be the stability of the resulting compound.

Striking confirmation of this theory was obtained almost at once by Perkin, who succeeded in preparing a compound containing the *cyclopentane* ring. By condensation of two molecules of malonic ester with one of trimethylene bromide, he obtained a tetracarbethoxypentane

whose sodium derivative, when treated with iodine, gave ethyl 1,1,2,2-cyclopentanetetracarboxylate.



Hydrolysis of the ester gave an acid which when heated lost carbon dioxide and yielded 1,2-cyclopentanedicarboxylic acid.

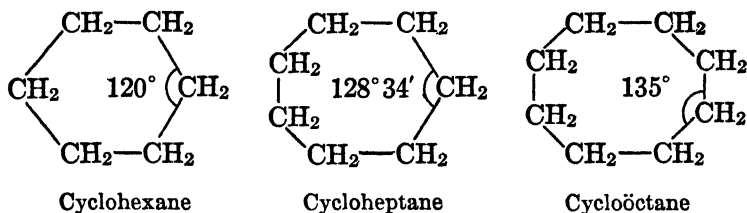


It should be pointed out that according to Baeyer's theory the cyclopropane ring, since it possessed greater strain, should be less stable than the cyclobutane ring, and that the latter in turn should be less stable than the cyclopentane ring. The 1,2-cyclopentanedicarboxylic acid was indeed found to be extremely stable, completely fulfilling the predictions of the theory.

It may be said at once that for hydrocarbons having rings smaller than that of cyclohexane the theory of Baeyer is in fairly satisfactory agreement with the facts which are known at the present time, although the physical character of the strain is not yet fully understood.

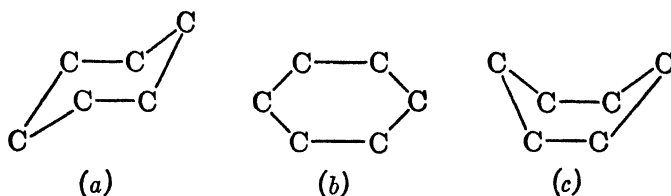
### Strainless Rings

An integral part of Baeyer's strain theory was that the carbon atoms of the ring must lie in a plane, and on this basis he predicted that the formation of large rings would involve *negative* strain. From an inspection of the following figures it is evident that in cyclohexane and compounds containing larger rings the planar configuration requires that the angle formed by the valence bonds be somewhat greater than normal and that the amount of this stretching increases proportionately to the size of the ring.



This postulate was supposed to account for the fact that rings of more than six members had not been made or discovered in nature and were presumably very unstable. Moreover, it implied that very large rings would be incapable of existence.

This part of Baeyer's theory has proved to be misleading if not entirely erroneous. Sachse was the first to perceive that the so-called negative strain need not exist and that the large rings might be, in fact, strainless. This idea was disregarded by chemists for nearly thirty years but was eventually revived and elaborated by Mohr, and within recent years has been almost fully confirmed by experiment. The idea of Sachse may be illustrated by reference to models. When, by the use of tetrahedral atoms, models are constructed for rings containing more than five members it is found that the atoms forming the ring do not lie in a plane. For example, six tetrahedral atoms may be united as shown in *a* or *c*.

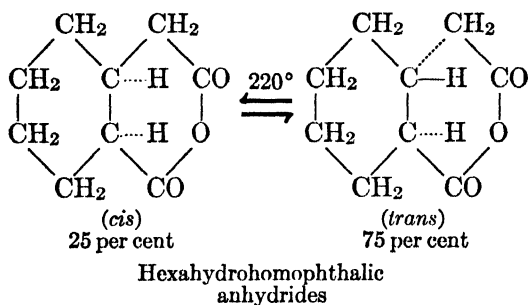


These models differ from the planar one shown in *b* in that they can be constructed without distortion of the tetrahedral form of the atoms involved. For the atoms to be in a plane as in *b*, it is necessary, as noted earlier, to introduce negative strain, i.e., increase the angle between the annular bonds to values greater than the normal.

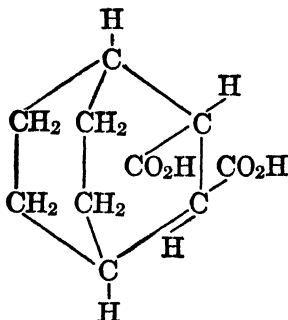
Since stable rings are now known which contain more than thirty members there is no necessity for assuming a planar form for any ring of more than five members. Rings of the nonplanar type are known as *strainless rings*.

The strainless models for cyclohexane shown in *a* and *c* are called, respectively, the "chair" (or Z) and "boat" (or C) forms. As yet there is no evidence that such forms exist in simple rings but many bicyclic compounds are known whose structures must be of these types. Thus both the *cis* and *trans* 1,2-dicarboxylic acids of cyclohexane form anhydrides.

Hexahydrohomophthalic acid is especially interesting; at 220° the anhydrides of the *cis* and *trans* modifications exist in equilibrium and the latter form predominates.



The correctness of this explanation of the formation of monomeric anhydrides of the *trans* forms of dibasic acids of this type was confirmed by the discovery that the *trans* form of the endocyclic derivative of hexahydrophthalic acid, in which the rings are no longer free to move, cannot form an anhydride.



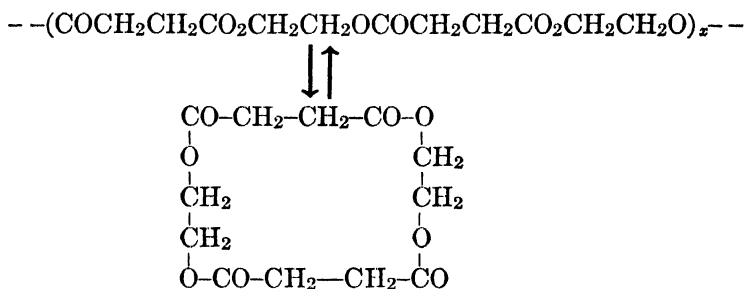
Compounds containing very large carbon rings have been found to possess stabilities comparable with those of the corresponding open-chain compounds. It should be mentioned, however, that even in these substances there is evidence that some strain persists.

### The Synthesis of Alicyclic Compounds

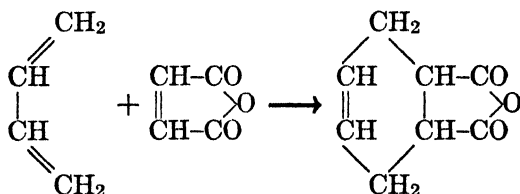
**Ring Closure.** Nearly any reaction involving the formation of a new carbon-to-carbon linkage can be used to form alicyclic rings from linear molecules. Some important examples already considered are the Dieckmann adaptation of the Claisen condensation, the Perkin method, the method of Ziegler, and the thermal decomposition of suitable dibasic acids or their salts.

The closure of large rings has been effected by use of the so-called dilution principle, which requires that the reactions be carried out in very dilute solutions. Obviously, the chances of intermolecular reaction are decreased by lowered concentration whereas those of intramolecular reaction are independent of concentration.

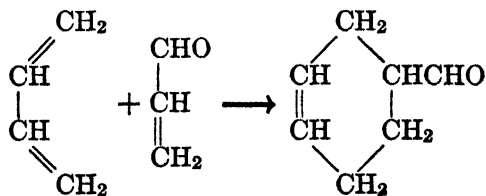
Large rings have been made also by taking advantage of the volatility of the products. Polyesters form reversibly, for example, and some of the cyclic forms are always present in equilibrium with the linear polymers. Slow distillation causes the equilibrium to shift as the ring compound distills. Thus the polyester from ethylene glycol and succinic acid yields a sixteen-membered cyclic ester when distilled *in vacuo* at 300°.



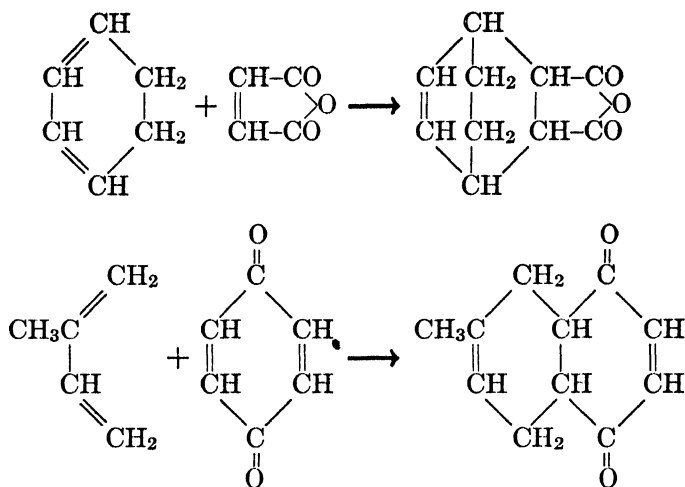
**The Diene or Diels-Alder Condensation.** Perhaps the most useful method for forming carbocyclic rings is the diene or Diels-Alder condensation. It may be illustrated by the condensation of maleic anhydride with 1,3-butadiene.



This synthesis provides a very general method for building six-membered rings. In place of maleic anhydride may be used many  $\alpha,\beta$ -unsaturated carbonyl compounds such as acrolein and benzoquinone. The reaction is so general for 1,3-butadienes that it is used as a test for the system of linkages  $\text{--C=C--C=C--}$ .





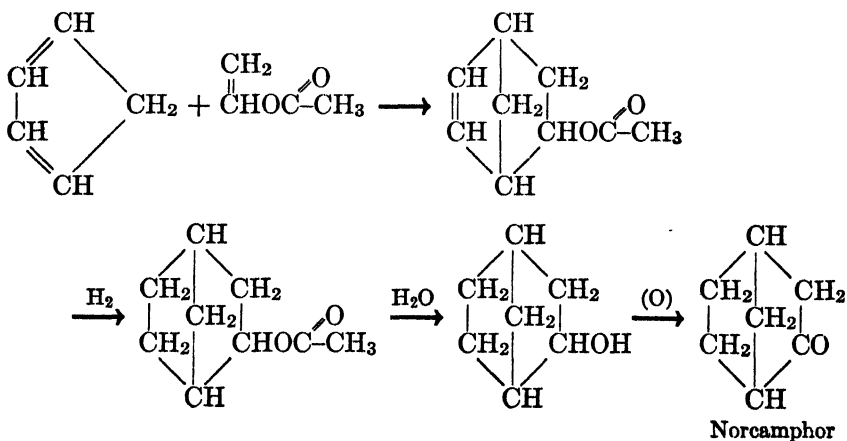


It will be noted that in these examples a 1,3-diene condenses with an olefinic compound in which the double bond is conjugated with a carbonyl group. To these may be added derivatives of cyanoacetic and acetoacetic esters of the following types.



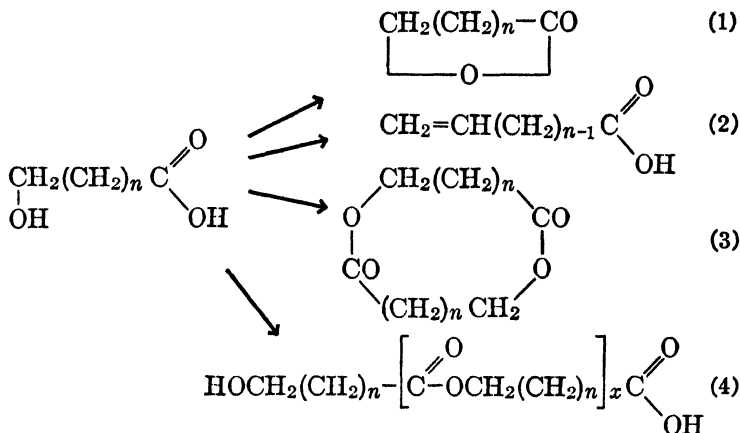
However, the synthesis is possible for many unsaturated compounds which do not belong to this category. Among these are styrene, vinyl chloride, vinyl acetate, and allyl chloride.

The condensation of vinyl acetate with cyclopentadiene affords an entry into the norcamphor series.



### The Closure of Non-Benzenoid Heterocyclic Rings

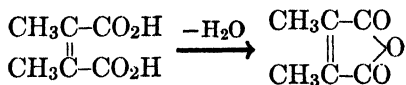
The various types of reaction possible in the case of bifunctional molecules are illustrated by the hydroxy acids, which, as has been stated, react differently depending on the distance between the functional groups.



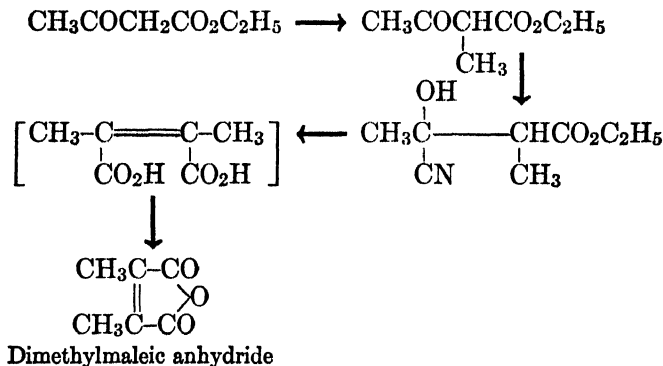
From a consideration of the molecular structure of hydroxy acids, reaction 1 or 3 is to be expected when a five- or six-membered ring would be formed. Otherwise reaction 4 is the normal one. Reaction 2 takes place only in the case of  $\beta$ -hydroxy acids. Lactone formation as in reaction 1 occurs when  $n = 2$  or 3. The formation of a double bond (reaction 2) takes place when  $n = 1$ . When  $n = 0$  the double lactone (lactide) forms. In all other cases ( $n > 3$ ) reaction 4 predominates.

In addition to lactones there are many other non-aromatic heterocyclic types which are familiar. Among these are acid anhydrides, lactams, cyclic acetals, cyclic ketals, and imides.

An interesting example is dimethylmaleic anhydride. Dimethylmaleic acid is so unstable that it has never been isolated. The anhydride is formed spontaneously.



This anhydride also can be used in the Diels-Alder condensation. The synthesis of dimethylmaleic anhydride is carried out in the following way:



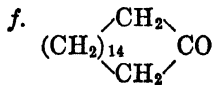
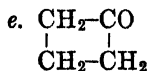
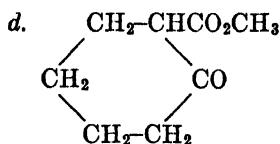
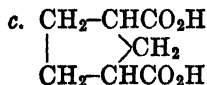
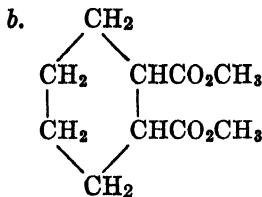
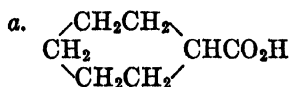
## PROBLEMS

1. Show by examples how the following types of reaction can be used to close alicyclic rings:

- |                         |                       |
|-------------------------|-----------------------|
| a. Diene synthesis      | c. Dieckmann reaction |
| b. Malonic ester method | d. Ziegler method     |

2. What structural characteristics must a molecule possess in order to undergo cyclization?

3. Outline methods for making the following substances from open-chain compounds:



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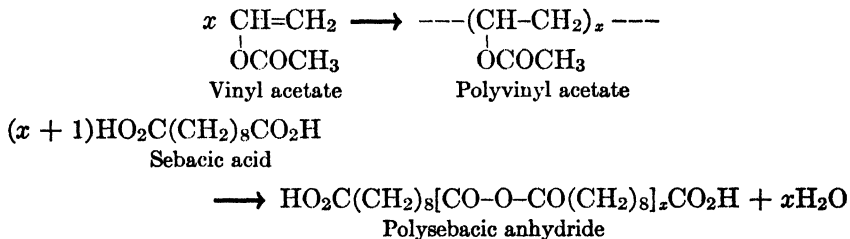
## CHAPTER XXVII

### POLYMERIZATION AND POLYMERS

#### Definitions

The terminology in this rapidly developing field is gradually becoming standardized along the lines indicated in the discussion of polyvinyl chloride (p. 24), polyesters (p. 138), and other polymers. It is important to have a precise understanding of the meaning of the terms to be employed and for this reason a recapitulation of definitions is given here.

A *polymer* is a molecule of very high molecular weight, made up of a particular recurring structural unit or type of unit. Reactions which lead to the formation of polymers from small molecules are called *polymerization*. These terms are illustrated by the following examples:

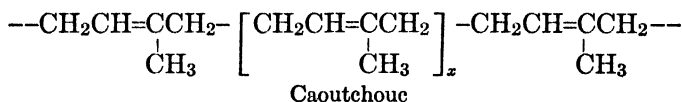


Carothers defined polymerization as *a reaction which is functionally capable of proceeding indefinitely*. It will be noted that in both of the examples the polymer possesses the same functional capacity for reaction as the monomer. If the reaction proceeds by simple addition as in the case of polyvinyl acetate the process is called *addition polymerization*. The formation of polysebacic anhydride illustrates a second type of polymerization known as *condensation polymerization*. In this type some small molecule such as water or alcohol is formed along with the polymer.

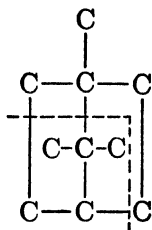
#### Natural Polymers

There are many natural polymers or giant molecules. Nature turns to these for the building of strong or rigid structures. Among the most important natural polymers are caoutchouc or unvulcanized rubber, proteins, and cellulose.

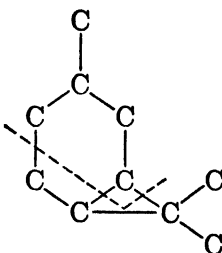
Caoutchouc is composed of the isoprene unit repeated over and over. The polymer has a molecular weight of about 64,000–88,000, i.e., it contains 900–1300 isoprene units.



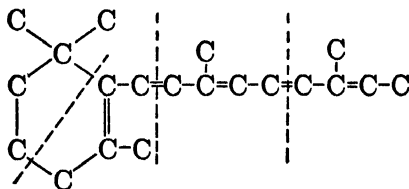
It is of great interest to note that the *terpenes* and related groups of naturally occurring substances may be thought of as constructed of isoprene units. This may be seen from the following skeletal structures of camphor, carane, and vitamin A.



Camphor

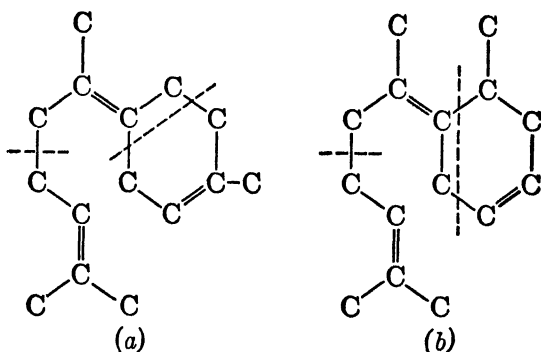


Carane

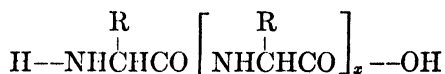


Vitamin A

The occurrence of isoprene units is so general that investigators of the structures of natural products generally consider the most probable formula of an unknown compound to be that which contains the maximum number of isoprene units. This is called the "isoprene rule"; it has been very useful in the determination of the structure of natural products. Its use can be illustrated by the case of the sesquiterpene bisabolene. It has the formula  $\text{C}_{15}\text{H}_{24}$  and has one ring and three olefinic linkages. Ozonization converts it into succinic acid, acetone, and levulinic acid. These data do not permit a decision to be made between formulas *a* and *b*. The isoprene rule, however, eliminates formula *b* as a probability.

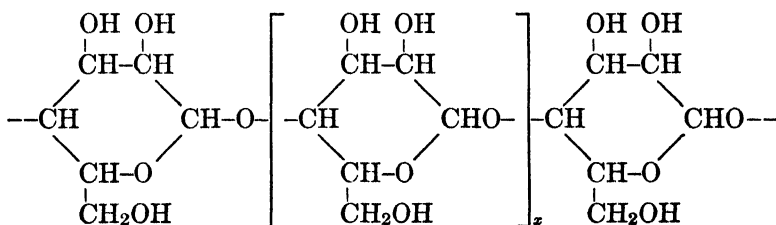


Proteins are natural polymers but differ from others in that they contain a variety of different structural units. However, all these are of the same type— $\alpha$ -amino acids—and the polymers may be represented as follows:



Their molecular weights vary from 34,000 for egg albumen to about 50 million for the filterable virus from tobacco mosaic.

Cellulose can be hydrolyzed to glucose, and is believed to consist of anhydroglucopyranose units (p. 200). The polymer is thought to be a polyacetal of the following type:



### Synthetic Polymers

Although none of the natural polymers has been synthesized as yet, chemists have been able to imitate them and in most instances to improve upon them by synthesis. Indeed, the thousands of known synthetic polymers offer a vast array of types affording almost any desired combination of properties. For economic reasons most of these are unable to compete with natural polymers, but a large number are now in daily use; in 1940, 500,000,000 lb. of synthetic polymers was sold. Some of these polymers will now be described briefly.

### Addition Polymerization

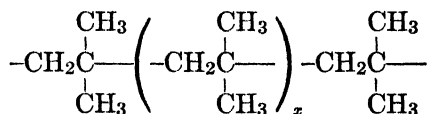
A great variety of substances containing one or more ethylenic or acetylenic linkages undergo polymerization. The conditions required to bring about the reaction vary, however, with the number and position of such linkages, as well as with the nature and position of other functional groups in the molecule.

**Ethylene.** When ethylene is heated with a small amount of oxygen to temperatures of 100–400° and under pressures exceeding 1000 atmospheres, a transparent, solid polymer is formed. It is primarily a straight-chain hydrocarbon of the following type:

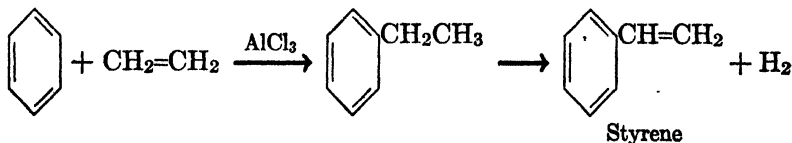


This material is produced in England in commercial quantities, under the name Polythene. It is used as an insulator in high-frequency and co-axial cables.

**Isobutylene.** The process mentioned earlier (p. 31) for converting isobutylene to liquid hydrocarbons of the gasoline range involves dimerization rather than true polymerization. Under the influence of certain catalysts, such as boron fluoride, isobutylene is converted to polymers of high molecular weight. The lower polymers are viscous liquids which find use as viscosity stabilizers for lubricating oils. Higher polymers are tough elastic solids, useful as rubber substitutes. The substances are probably long chain hydrocarbons with the following type of structure:



**Styrene.** Styrene, or phenylethylene, is present in coal tar but is now produced synthetically from benzene and ethylene. Ethylbenzene is made from these by the Friedel-Crafts method and is then dehydrogenated.

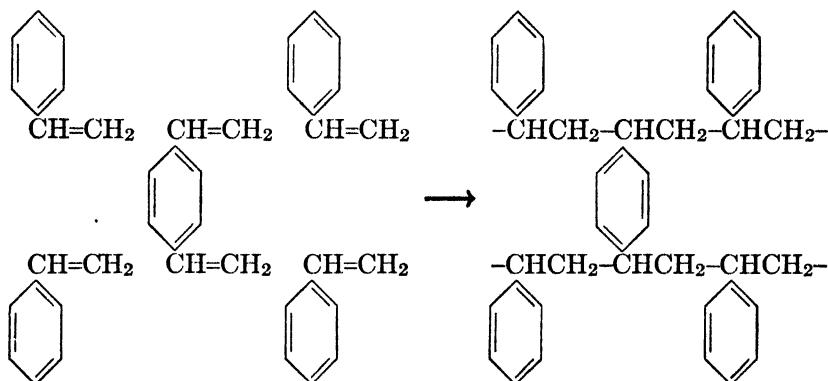


It is generally true that a "negative" or unsaturated group, such as phenyl or carbonyl, attached to an olefinic carbon atom, increases the tendency to polymerize. Styrene,  $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$ , polymerizes very readily. The reaction may be catalyzed by organic peroxides or by light, or it may be carried out thermally. In order to store styrene it is

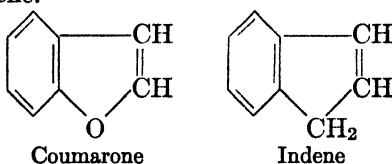
necessary to add a small amount of a reducing agent, such as hydroquinone.

Polystyrene is a highly transparent, colorless solid. It is an excellent insulating material and is used in coating compositions as well as in moldings.

If the styrene used contains small amounts of divinylbenzene the hardness of the polymer is increased. This is probably due to the fact that divinylbenzene can enter two polymeric chains, thus introducing cross links (p. 126). This possibility is shown in the following representation.



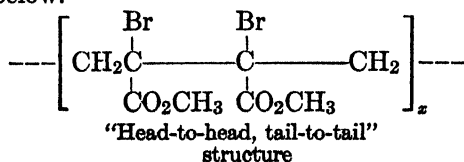
Coumarone and indene, isolated from coal tar, may be regarded as derivatives of styrene.



Like styrene, they can be polymerized. The coumarone-indene polymers have found extensive uses in the manufacture of floor coverings, oil cloths, and adhesives.

**The Acrylates.** The most important polymers of the acrylate type are polymethyl methacrylate (p. 146) and polymethyl acrylate (p. 146).

The polymer of methyl  $\alpha$ -bromoacrylate is of particular interest because it appears to have the "head-to-head, tail-to-tail" type of structure indicated below.

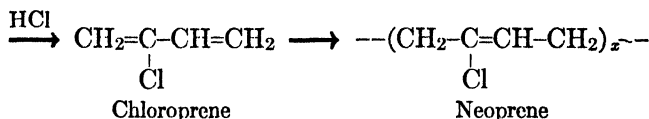






Among the most important of the synthetic rubbers in current use are Neoprene and the Buna rubbers.

**Neoprene.** Neoprene is a polymer of chloroprene, which, as indicated earlier (p. 27) is prepared from acetylene and hydrogen chloride.



The molecule is very similar to that of caoutchouc, a chlorine atom having replaced the methyl group. The properties of Neoprene resemble those of rubber. However, unlike rubber, Neoprene does not have to be vulcanized, and it does not imbibe liquids. About 1,000,000 lb. of Neoprene was sold in 1937. Neoprene is unsuitable for automobile tires because of its greater weight.

**Buna Rubber.** 1,3-Butadiene polymerizes in contact with sodium at 35–40° to give Buna rubber. In the name, “bu” refers to butadiene and “na” to sodium (*natrium*). The polymerization can be effected by other means, and the word Buna is now applied to butadiene rubbers more or less generally (p. 27).

In recent years the quality of butadiene rubbers has been greatly improved through the development of *copolymers*. Buna S is a copolymer of the diene and styrene. In resistance to heat and abrasion it is superior to natural rubber; it is, accordingly, used in the manufacture of tires. Perbunan (Buna N) and Perbunan Extra are copolymers of the diene and acrylonitrile. They differ in the acrylonitrile content, the Perbunan Extra containing about thirty per cent of this constituent. Their important characteristics are resistance to abrasion and to swelling by petroleum oils.

One of the most significant developments in the production of synthetic rubbers has been the introduction of emulsion polymerization. The material to be polymerized is emulsified in water, usually with the aid of a soap or other detergent and in the presence of a protective colloid. The emulsion is homogenized, and polymerization is effected by addition of a peroxide, the salt of a peracid, or other substance which readily liberates oxygen. A colloidal suspension of the polymer is obtained, and it is processed in much the same way as the natural rubber latex. Neoprene, Buna S, and the Perbunans are all produced by the emulsion technic.

Although synthetic rubbers have been in use in Europe for many years, particularly in Germany, they have not yet been used in the

large-scale production of American automobile tires. However, the production of butadiene from butane (p. 27) may enable the Buna rubbers to compete with the natural variety in the western hemisphere.

**Butyl Rubber.** Because natural rubber is unsaturated, it was long thought that synthetic rubbers of a similar structure would most closely resemble the natural material. This accounts largely for the development of the synthetic diene rubbers. However, some of the undesirable properties of natural rubber, such as its deterioration through oxidation by the air, are to be ascribed to the presence of reactive olefinic bonds. It is now known that certain saturated polymers, e.g., polyisobutylene and Thiokol (p. 366), have many of the properties of rubber. Indeed it appears that the only desirable characteristic of natural rubber which is definitely related to unsaturation is the reaction with sulfur. A small percentage of the unsaturation is lost during sulfur vulcanization; it is believed that the process involves cross linking of the hydrocarbon chains by reaction with the sulfur. From these considerations it has been deduced that the copolymerization of a small amount of a diene, such as butadiene, with an olefin, such as isobutylene, should give a rubber with just enough unsaturation to permit vulcanization. The new butyl rubber is a copolymer of this type. The vulcanized material is almost completely saturated and has unusually high resistance to attack by oxygen and chemical agents.

### The Mechanism of Addition Polymerization

Addition polymerization probably involves a chain reaction set off by an activated molecule of monomer. The absence of dimers, trimers, and other products of low molecular weight, even at the beginning of the reaction, seems to preclude the theory of stepwise polymerization.

The catalysts used to bring about this type of polymerization are usually peroxides such as benzoyl peroxide and hydrogen peroxide. Antioxidants such as hydroquinone are employed to preserve the monomers, since unsaturated compounds on exposure to the air form traces of organic peroxides.

The chain reaction theory of addition polymerization accounts for the fact that it is possible to control the size of the polymeric molecule by regulation of the amount of catalyst and temperature. According to this theory the reaction is initiated by combination of a molecule of monomer with a fragment of the catalyst; the resulting active particle combines with another molecule of monomer to yield a second active fragment. The process continues until the chain reaction stops, as, for

example, by combination of two active chains or collision of the active chain with a catalyst fragment.

According to these views, as the amount of catalyst is increased the number of growing chains started will also increase. The monomeric molecules must therefore divide themselves among a larger number of polymeric chains, and the molecular weight of the polymer will decrease. Actually, it is found that polymers of highest molecular weight are obtained with minimal amounts of catalyst. Similarly, in polymerization by heat, in which the active fragments are generated thermally from the monomers, the largest polymeric molecules are obtained at the lowest temperatures.

It is interesting that two different monomers can be caused to polymerize together to form copolymers. In some instances a substance which itself will not undergo polymerization can be induced to copolymerize. Thus maleic anhydride does not polymerize alone but if styrene is polymerized in the presence of maleic anhydride the polymer contains units of both the anhydride and styrene. This type of polymer is called a *heteropolymer*.

### Condensation Polymerization

Any reaction which leads to the combination of two molecules or parts of two molecules may be adapted to the preparation of polymers. It is only necessary that each reacting molecule be capable of reaction at two or more points. Condensation polymers may be produced from a great variety of polyfunctional compounds; examples which have been mentioned are the aldehyde resins (p. 313), the urea-formaldehyde resins (p. 126), the polyesters (p. 138), the polyamides (p. 140), the phenol-formaldehyde resins (p. 163), and the polyanhydrides (p. 136).

Various general types of molecules capable of undergoing condensation polymerization may be distinguished. For example, in bifunctional molecules the two functional groups may be alike. The formation of polyanhydrides from dibasic acids is illustrative; similarly, polyethers may be obtained from glycols. It is also possible to polymerize certain bifunctional molecules in which the two groups are different. The polyesters derived from hydroxy acids (p. 138) illustrate this type. The most important commercial condensation polymers are obtained from mixtures of two compounds, each of which has two or more functional groups of the same type. The polyamides and the *alkyds* (Glyptals) are of this type.

Condensation polymerizations ordinarily proceed by the same mechanism as do the corresponding reactions between monofunctional compounds. Since no chain reactions are involved, the reaction would be

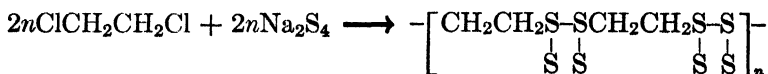
theoretically complete only when all the monomeric units present had been incorporated into one giant polymeric molecule. Actually, the molecular weights of condensation polymers are usually much lower than those of addition polymers. Various factors are responsible. Among the most important is the increasing viscosity and consequent difficulty in removing the second product (usually water) as the polymerization proceeds.

In general, if all the molecules participating in a condensation polymerization are bifunctional, the product will be a linear polymer. The commercial polyamides (p. 140) and Thiokol are examples. If one or both of the reacting molecules has more than two functional groups a cross linked polymer is formed. The glycerol-phthalic anhydride resins, the Bakelites, and the urea-formaldehyde resins are in this category. The first and second of these each have one component (glycerol and phenol, respectively) capable of reacting at three points. Urea has four hydrogen atoms capable of reacting with formaldehyde and thus may be regarded as tetrafunctional. Formaldehyde is peculiar in that although only one functional group reacts (the carbonyl group), it can react with two molecules of phenol or urea.

Most of the addition polymers are of the type known as "*thermo-plastic*," that is, they soften on heating. Some of the condensation polymers, e.g., Nylon (p. 140), are of the same type. The molding of the polymethacrylate and polystyrene resins and the extrusion of Nylon into fine threads take advantage of this phenomenon. Other condensation polymers are described as "*thermosetting*" or "*heat convertible*." Polymers which can form cross links are in this group. On heating they undergo further cross linking, with the result that the molecule becomes more complex. The resulting products are insoluble and infusible.

A few of the more important condensation polymers are discussed below. These are selected partly to illustrate the principles mentioned above and partly because of their commercial value.

**Thiokol.** The Thiokol resins are produced from sodium tetrasulfide, chlorine, and the waste olefin gases from cracking stills. They are made chiefly from ethylene chloride according to the following equation:



The nature of the groups at the ends of the polymeric chain is determined by the ratio of the two reactants. Thus, if ethylene chloride is used in excess, the terminal groups should be  $-\text{CH}_2\text{CH}_2\text{Cl}$ ; if the tetrasulfide is present in excess, the end groups should be  $-\text{S}-\text{S}-\text{Na}$ . The properties



of the polymeric material obtained in the one case are strikingly different from those of the polymer produced in the other. A viscous liquid is obtained by the use of an excess of ethylene chloride, and a tough rubber-like material by the use of an excess of sodium tetrasulfide. The difference has been explained on the assumption that the terminal  $-S-S-Na$  groups degenerate to  $-SH$  or  $-SNa$  groups and that these

$\begin{array}{c} | \\ S-S \\ | \end{array}$   
are oxidized to  $-S-S-$  groups by the excess sodium tetrasulfide. Thus, two reactions are involved in the chain-lengthening process. Thiokol rubber is vulcanized by the action of zinc oxide. It is probable that the reaction is again one of oxidation, bringing about still further increase in the length of the chains.

The major uses of Thiokol are in the fabrication of flexible tubes and linings for tanks used in the oil industry. Its resistance to the solvent action of hydrocarbons makes it superior to natural rubber for such purposes.

**Nylon.** The preparation of Nylon from adipic acid and hexamethylenediamine has been discussed. Similar polyamides have been prepared from other combinations of dibasic acids and diamines, but not, up to the present, in commercial quantities. These materials are linear polymers.

**Phenol-Formaldehyde Resins.** When a mixture of phenol and paraformaldehyde is heated with a catalyst a cross linked, insoluble polymer is produced directly (p. 163). If aqueous formaldehyde is used, a less complex resin can be obtained. This product is thermosetting, indicating that it contains methylol ( $-CH_2OH$ ) groups which react further on heating to give the cross linked polymer. Bakelite molding compositions are made by powdering the resin, usually with a filler such as wood flour. When heated under pressure in the mold the material hardens and takes the shape of the mold.

Bakelite resins are modified in various ways. Other aldehydes, such as furfural, may be used. The amount of cross linking may be reduced by adding an *ortho*- or *para*-substituted phenol, such as *o*- or *p*-cresol.

The Ciba resins resemble Bakelite. They are prepared from aromatic amines and aldehydes. Because the aldehyde can react with the amino hydrogen atoms as well as those of the ring, the possibilities of cross linking are greater and the polymers are more complex.

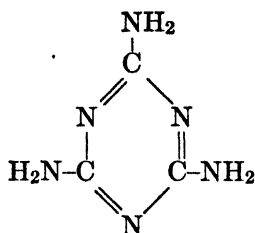
**Melamine-Formaldehyde Resins.** Melamine may be regarded as the trimer of cyanamide. Cyanamide (p. 127) is quite unstable and changes rapidly to dicyandiamide when liberated from its salts. When dicyandiamide is heated under suitable conditions it changes to melamine.



Cyanamide



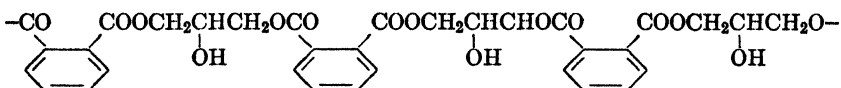
Dicyandiamide



Melamine

Melamine reacts with formaldehyde to give methylol derivatives which are transformed to thermosetting resins on heating. The reactions involved are probably of the same type as those already discussed (p. 126) in connection with the urea-formaldehyde resins. However, since melamine has three amino groups as compared with the two in urea, the structure of the polymer is more complex.

**Polyesters.** The most important polyesters are the *alkyd* resins made from phthalic anhydride and glycerol (p. 366). The primary hydroxyl groups of glycerol are more reactive in ordinary esterifications than is the secondary group. It would be expected, therefore, that these would react first with phthalic anhydride. This appears to be true, for soluble polymers can be obtained by regulating the amount of phthalic anhydride or by controlling the temperature of the reaction. These products appear to be linear polymers of the following type:



The modified alkyds are produced by carrying the polymerization to the stage indicated and esterifying the secondary alcohol group with a monobasic acid (p. 84). If phthalic anhydride is used in excess of the amount indicated in the formula above and if the reaction is interrupted just before gelation occurs, the "heat-convertible" resins are produced. These apparently contain  $\text{--COC}_6\text{H}_4\text{CO}_2\text{H}$  groups in place of some of the secondary hydroxyl groups. On heating these react with hydroxyl groups in adjacent chains to introduce cross links.

## PROBLEMS

1. Define polymer, copolymer, heteropolymer, thermoplastic polymer, thermosetting polymer, vinyl polymer, alkyd resin, chain reaction.
2. Distinguish between condensation polymerization and addition polymerization.
3. What is the isoprene rule, and how is it used?

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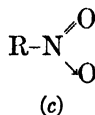
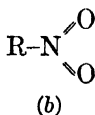
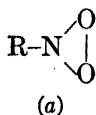


## CHAPTER XXVIII

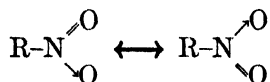
### NITRO COMPOUNDS

#### The Structure of the Nitro Group

Three formulas have been advanced for the nitro group.

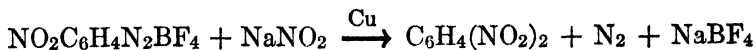
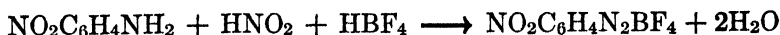


Formula *a* has been abandoned because it does not explain the great stability of nitro compounds and in particular gives no suggestion as to the similarity between the groupings  $\text{RCH}_2\text{CO}-$  and  $\text{RCH}_2\text{NO}_2$ . Formula *b* gives the nitrogen atom a covalence of five. Since no compound is known in which nitrogen exhibits this valence, this structure is less satisfactory than that represented by formula *c*. It is also clear that formula *c* is unsatisfactory in that it is unsymmetrical. *p*-Dinitrobenzene has a small dipole moment showing that the nitro group must be symmetrical. The symmetry is due to resonance.



#### Synthesis of Nitro Compounds

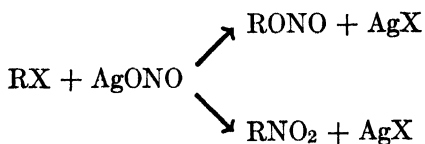
Aromatic nitro compounds are made by direct nitration with nitric acid, usually in the presence of sulfuric acid. This process is governed by the usual rules of orientation and as a consequence does not always permit the introduction of the nitro group into the desired position. In such cases other methods must be used. For example, nitration of nitrobenzene gives almost exclusively *m*-dinitrobenzene. To obtain *o*- or *p*-dinitrobenzene an indirect method is required. These compounds may be obtained from the corresponding nitroanilines by diazotization and treatment with excess nitrous acid in the presence of cuprous oxide. A better method is to treat the diazonium borofluoride with sodium nitrite in the presence of copper powder.



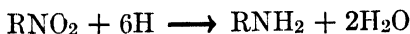
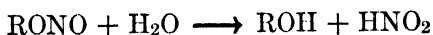
A similar method is used for making  $\beta$ -nitronaphthalene.

*m*-Nitrotoluene is formed in small amounts in the manufacture of the *ortho* and *para* isomers by nitration of toluene. In the purification of the latter the *meta* isomer is separated, and thus is available in considerable amounts.

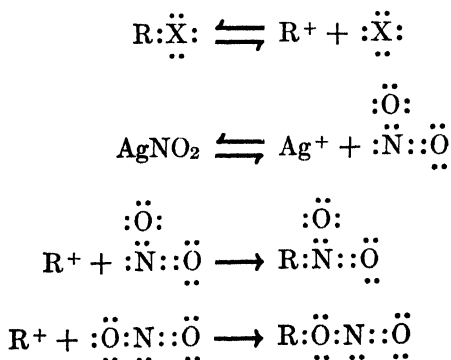
Aliphatic nitro compounds were first made by the action of silver nitrite on alkyl halides. This reaction produces a mixture of the corresponding alkyl nitrites and nitroparaffins.



If  $\text{R} = \text{CH}_3$ , nitromethane is the sole product, but for larger radicals the nitrite predominates. The two types are differentiated by the fact that the nitrite is easily hydrolyzed to an alcohol and the nitro compound is readily reduced to an amine.

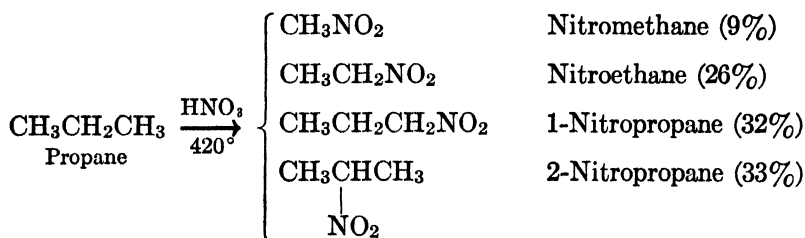


The course of the reaction between an alkyl halide and silver nitrite is understood somewhat better by reference to the following mechanism.

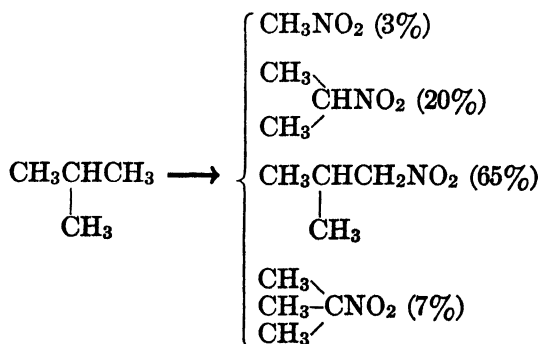


Paraffins and cycloparaffins yield nitro derivatives when subjected to prolonged treatment with dilute nitric acid. At low temperatures the reaction is too slow to be useful and at high temperatures oxidation

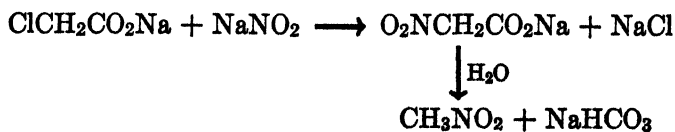
occurs. A vapor phase nitration of paraffins has been developed that affords satisfactory yields of several of the simplest nitroparaffins. It involves momentary contact of the hydrocarbon with nitric acid at temperatures near 400°. Pyrolysis and nitration both occur. Ethane is converted to nitroethane and nitromethane in yields of 73 and 27%, respectively. Propane gives rise to a mixture of nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane (p. 12).



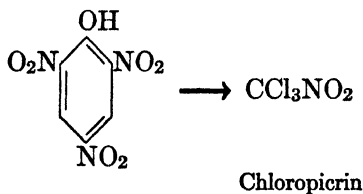
The mechanism of the nitration of paraffins at elevated temperatures is not well understood. Since nitric acid is completely dissociated at 250°, the reaction evidently involves oxides of nitrogen. The products obtained are those theoretically derivable from the free radicals which would be produced by chain cleavage or by loss of hydrogen. For example, isobutane yields the four nitro compounds which would be predicted on the basis of this mechanism.



*Nitromethane* can be made by treating sodium chloroacetate with sodium nitrite. Nitroacetic acid is unstable and breaks down to carbon dioxide and nitromethane.



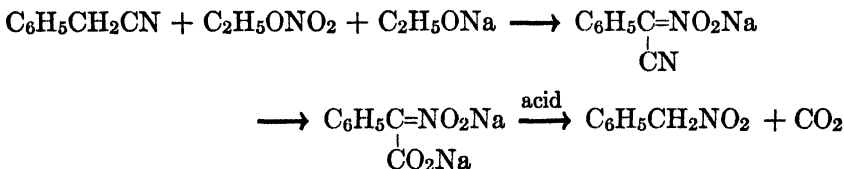
The trichloro derivative, known as *chloropicrin*, can be made in a variety of ways. One method involves the treatment of picric acid with calcium hypochlorite.



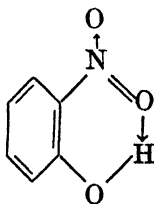
This substance is an important lethal gas and is used in warfare. It is fatal to man when breathed in concentrations of 1/20,000.

*Tetranitromethane* is made from acetic anhydride and fuming nitric acid. In petroleum ether this compound gives intense colorations with all compounds having the vinyne linkage,  $-C\equiv C-$ .

*Phenylnitromethane* is made from benzyl cyanide, ethyl nitrate, and sodium ethoxide.

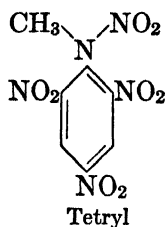
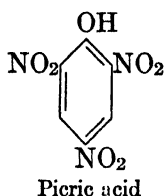
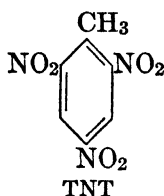


Nitration of phenol gives a mixture of *o*-nitrophenol and *p*-nitrophenol which can be separated by steam distillation. The *ortho* isomer is volatile and the *para* one is not. Similar differences in volatility have been noted in many cases and are believed to be due to chelation of the *ortho* isomers (p. 210).



## POLYNITRO AROMATIC COMPOUNDS

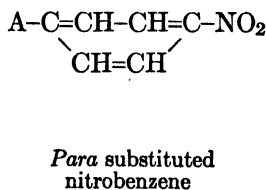
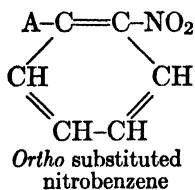
Polynitro aromatic compounds are of especial interest because they are explosive. The most important military high explosives are to be found in this group of substances. Examples are trinitrotoluene (TNT) (p. 39), picric acid, and tetryl.



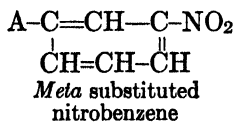
The chemistry of substances of this class is of great theoretical value also. The introduction of a number of nitro groups into an aromatic ring invariably brings about profound changes in the reactivity of the nucleus and of the substituents which it holds. As will be seen, these effects make possible many important synthetic methods. It will be convenient, therefore, to consider them at this point.

### Reactions of Derivatives of Polynitrobenzenes

The most significant characteristic of the influence of a nitro group on the chemical properties of aromatic nitro compounds is that it is exerted chiefly on the atoms or groups which are in positions that are *ortho* or *para* with respect to the nitro group. By reference to the vinylogy principle (p. 335) it is easy to see why this is so. Atoms or groups that are in positions *ortho* or *para* to each other are joined by one and two vinylene groups, respectively. Accordingly, they will behave, qualitatively at least, as though they were united directly. This means that the *ortho* and *para* nitrophenyl radicals are like acyl groups.



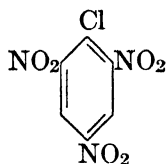
No such relationship is possible in *meta* compounds.



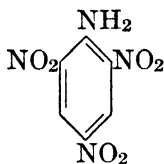
This comparison of *ortho* and *para* compounds with the corresponding *meta* isomer explains not only the differences observed between *ortho* and *para* compounds on the one hand and *meta* compounds on the other but also affords a basis for predicting the nature of the activation effect. If A is chlorine, for example, the compound will have the properties of

an acid chloride. That this is so is abundantly attested by the behavior of such compounds as *o*-nitrochlorobenzene, 2,4-dinitrochlorobenzene, and 2,4,6-trinitrochlorobenzene. In each, treatment with alkali causes the chlorine atom to be removed by hydrolysis and yields the salt of the corresponding phenol. Moreover, as the number of nitro groups increases the ease with which this replacement occurs is enhanced. The trinitro compound, in fact, is readily hydrolyzed by water. Because of this property it is known as picryl chloride—the chloride of picric acid.

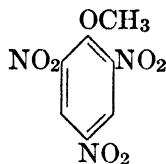
The reactions of picryl chloride are very similar to those of acid chlorides. Ammonia converts it into the corresponding amino compound which, because of its resemblance to amides, is known as picramide. Methanol replaces the chlorine atom with the methoxyl group, yielding trinitroanisole. The methoxyl group is readily attacked by hydrolytic agents—a fact that strengthens the analogy between this compound and esters.



Picryl chloride



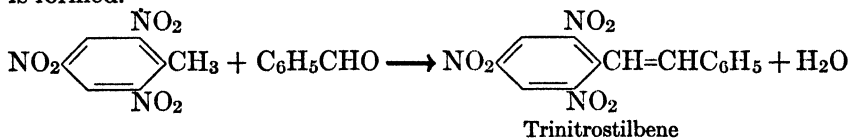
Picramide



Trinitroanisole

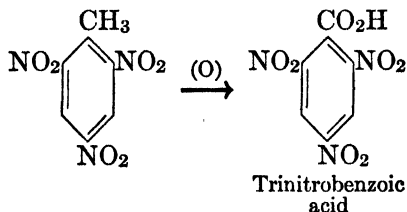
The reactivity of the chlorine atom in picryl chloride and similar substances is apparent also in the ease with which they undergo the Ullmann coupling reaction (p. 251).

TNT is a vinylog of nitromethane and, accordingly, should have an active methyl group. This agrees with the facts. When TNT is heated with benzaldehyde in the presence of an alkaline catalyst, trinitrostilbene is formed.



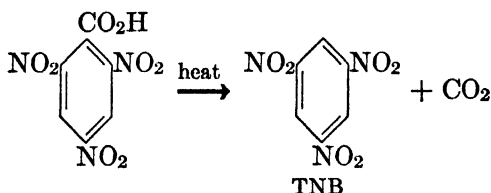
Trinitrostilbene

The reactivity of the methyl group in TNT is shown also by the fact that it is easily oxidized to trinitrobenzoic acid.



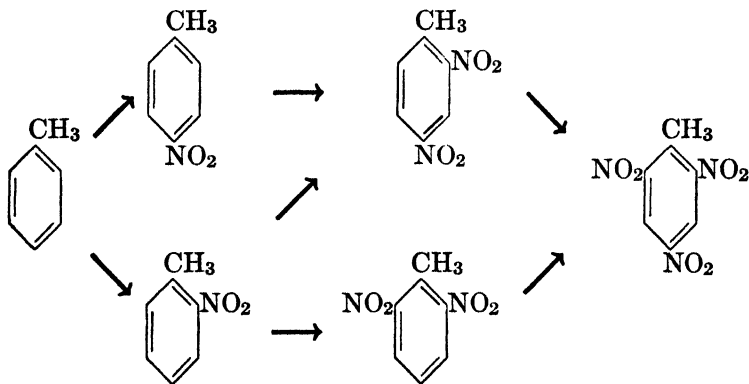
Trinitrobenzoic acid

2,4,6-Trinitrobenzoic acid might be expected to behave as an  $\alpha$ -keto acid. This analogy is borne out; this acid loses carbon dioxide at temperatures below  $100^\circ$  and yields 1,3,5-trinitrobenzene (TNB).

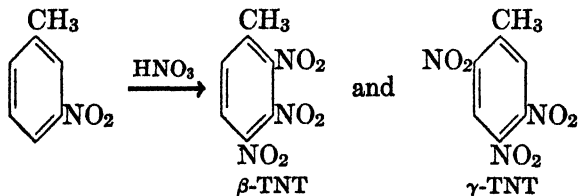


If the 1,3,5-trinitrophenyl radical is thought of as an acyl group, then TNB should behave as an aldehyde. It does, in fact, yield picric acid when oxidized with ferricyanides.

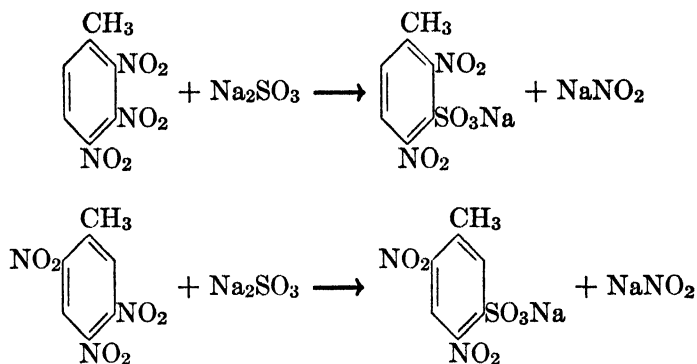
**TNT.** The most important high explosive is TNT. It is made by nitrating toluene. The nitration is carried out commercially in three stages. In the first stage mononitration occurs, yielding *o*- and *p*-nitrotoluenes. These are then converted to 2,4-dinitrotoluene. A small amount of the 2,6-isomer is also formed. Both the 2,4- and 2,6-isomers yield TNT in the last stage of the nitration.



Crude TNT contains small amounts of certain isomers which are produced by the nitration of *m*-nitrotoluene, a little of which is formed in the nitration of toluene (p. 371). Chief among these isomers is 2,3,4-trinitrotoluene or  $\beta$ -TNT (ordinary TNT is known as  $\alpha$ -TNT).

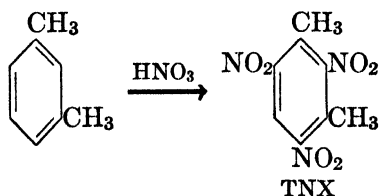


$\gamma$ -TNT, the 2,4,5-isomer, is formed in small amounts. These impurities can be removed from  $\alpha$ -TNT by washing with sodium sulfite solution, which rapidly converts them into water-soluble sulfonates.



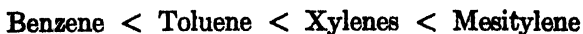
This method is of interest because it involves a replacement of a nitro group. It will be seen that the nitro group that is attacked in  $\beta$ -TNT is flanked on either side by other nitro groups and that the reactive group of  $\gamma$ -TNT is situated in a position which is *ortho* to one nitro group and *para* to the other. From what has been said, nitro groups so situated would be expected to be held loosely.

**TNX.** Trinitro-*m*-xylene (TNX) is prepared in much the same way as TNT. *m*-Xylene is more easily nitrated than is toluene. It is the only one of the xylenes that can be made to give a satisfactory yield of a trinitro derivative.



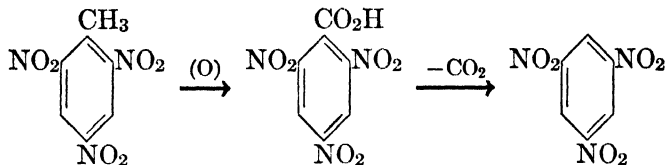
As a high explosive TNX is less powerful than TNT and is useful only when mixed with other materials such as ammonium nitrate. It is used also in commercial dynamites.

**TNB.** Direct nitration of benzene is not a satisfactory method for making the trinitro derivative. It is not difficult to obtain *m*-dinitrobenzene by this method but further nitration is very hard to accomplish. The ease of nitration of an aromatic hydrocarbon increases with the increase in the number of methyl groups as follows:





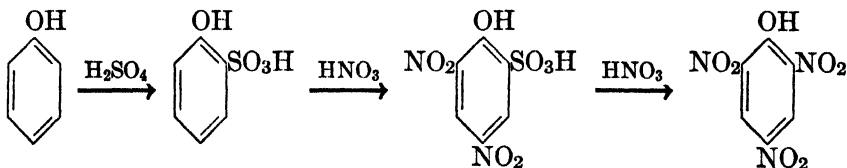
It is interesting that the value of the trinitro derivatives of these hydrocarbons as high explosives decreases with the increase in the number of methyl groups. TNB is more powerful than TNT which, in turn, is more powerful than TNX. It is unfortunate that TNB cannot be made cheaply. As a matter of fact, the best way to get it is to nitrate toluene and then remove the methyl group. This can be done by oxidizing TNT with chromic acid and decarboxylating the resulting acid.



**Picric Acid.** Picric acid is very widely used as a high explosive. One of the difficulties encountered in its use is that its melting point ( $122^\circ$ ) makes it hard to introduce into containers. For this reason, it is generally mixed with other similar nitro compounds such as 2,4-dinitrophenol and trinitro-*m*-cresol. The composition of the mixtures is such that they can be melted with steam.

Ammonium picrate and guanidine picrate are less sensitive to shock than is picric acid and are used with *boosters*.

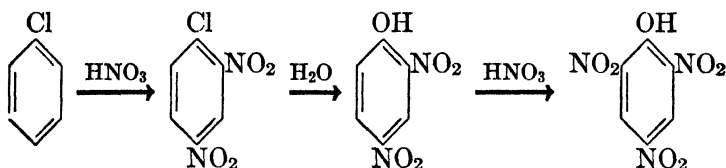
There are several methods for preparing picric acid. Direct nitration of phenol is attended with losses due to oxidation and is not a satisfactory method. In practice the phenol is first sulfonated and then nitrated. The sulfonic acid group makes the phenol less sensitive and is itself replaced by a nitro group at a certain point in the process.



The sulfonation leads to mixtures of *ortho* and *para* derivatives and may yield di- and even trisulfonic acids. This does not cause loss, however, since all these substances yield picric acid when nitrated.

It might be expected that picric acid could be made from chlorobenzene by nitration to produce picryl chloride which could then be hydrolyzed to the acid. Chlorobenzene is much more difficult to nitrate than is toluene and only the dinitro derivative can be made economically. Because of the influence of the nitro groups, however, the chlorine atom

in this compound can be replaced by a hydroxyl group by hydrolysis. The resulting dinitrophenol can then be nitrated to yield picric acid.

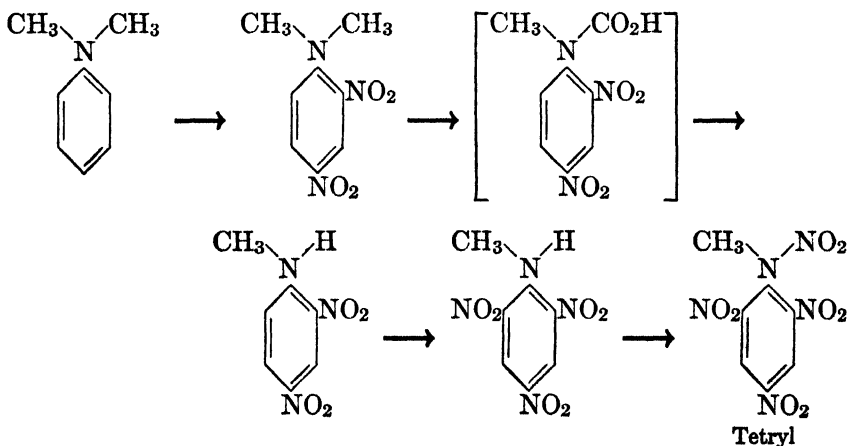


It has been mentioned (p. 244) that picryl chloride is made by treating picric acid with phosphorus pentachloride. This is yet another reaction that is to be ascribed to the influence of the nitro groups. It is a reaction that is characteristic of carboxylic acids rather than phenols.

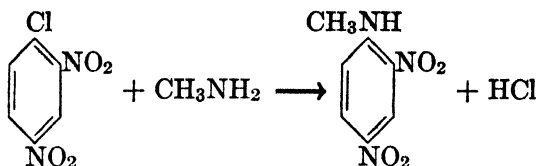
In the presence of mercuric nitrate, benzene can be nitrated and oxidized at the same time to yield picric acid in one step. The mechanism of this process is not clear, but it seems certain that the later stages of the nitration occur after a mercury salt of a nitrophenol has formed.

Picric acid unites with aromatic hydrocarbons and aryl ethers to give molecular addition compounds known as picrates. These are much used for purposes of identification.

**Tetryl.** Tetryl is a tetranitro derivative of methylaniline. It is manufactured from dimethylaniline by treatment with nitric acid in the presence of concentrated sulfuric acid. During the reaction, three nitro groups are introduced into the ring, and one of the methyl groups is replaced by a nitro group. The various processes take place in the following order:



2,4-Dinitromethylaniline can be made by the condensation of 2,4-dinitrochlorobenzene with methylamine.

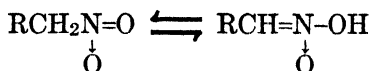


This offers another approach in the preparation of tetryl.

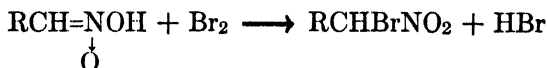
Tetryl is a more powerful explosive than either picric acid or TNT. It is likewise more sensitive to shock and finds use in boosters and detonators.

### Reactions of Nitro Compounds

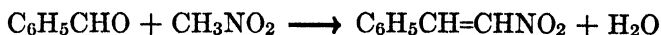
**Enolization.** A primary or secondary nitro compound may exist in an isonitro or *aci* form which is in equilibrium with the ordinary form.



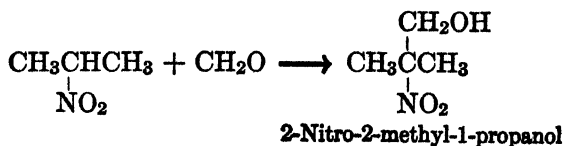
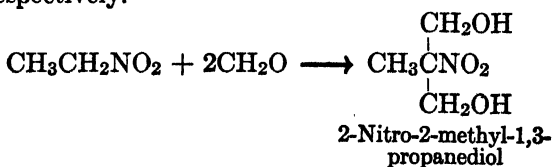
The isonitro form is acidic, whereas the nitro form is neutral. This suggests the keto-enol tautomerism observed with acetoacetic ester and similar compounds. The *aci* forms of primary and secondary nitro compounds are very easily brominated.



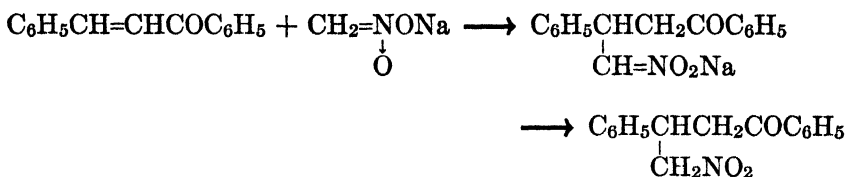
**Condensation.** Primary and secondary nitro compounds undergo condensations characteristic of active methylene compounds. For example, nitromethane reacts with benzaldehyde to give  $\beta$ -nitrostyrene.



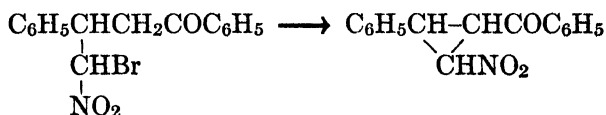
When primary and secondary nitro compounds are treated with formaldehyde in the presence of alkalies the active hydrogen atoms are replaced by methylol groups. Nitroethane and 2-nitropropane, for example, yield 2-nitro-2-methyl-1,3-propanediol and 2-nitro-2-methyl-1-propanol, respectively.



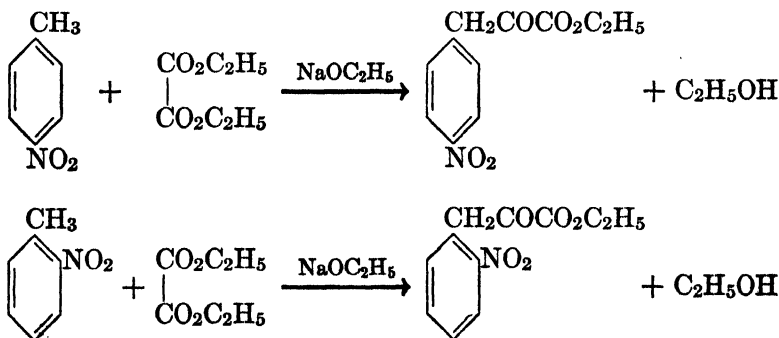
Reactions analogous to the Michael condensation are known also. Benzalacetophenone condenses with the sodium derivative of nitromethane in the following way:



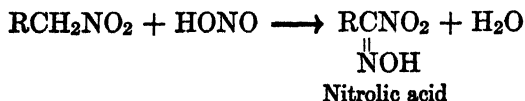
Bromination followed by treatment with potassium acetate gives a cyclopropane derivative.



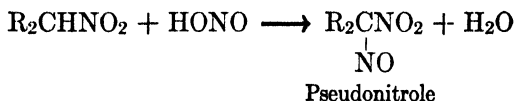
The comparison between nitromethane and its vinylogs, *o*- and *p*-nitrotoluene, is interesting. For these, in contrast to the *meta* isomer, possess active methyl groups. Commercial *m*-nitrotoluene is freed from traces of the *ortho* and *para* isomers by treatment with ethyl oxalate followed by steam distillation. The *m*-nitrotoluene is distilled, whereas the substituted pyruvic esters are nonvolatile.



**Reaction with Nitrous Acid.** Nitro compounds show conspicuous differences in their behavior toward nitrous acid depending on the number of  $\alpha$ -hydrogen atoms in the molecule. Primary nitro compounds have two active hydrogen atoms and react to give nitrolic acids.



Secondary nitro compounds, which have only one active hydrogen atom, form pseudonitroles.



Tertiary nitro compounds, of course, do not react. Salts of nitrolic acids are deep red in color. The pseudonitroles are really nitroso compounds and are colorless in the solid form but are blue in solution or in the fused state. This difference in color is characteristic of nitroso compounds, the colorless solid form being a dimer of the simple molecule which is blue. These colors form the basis of the "red, white, and blue" test for nitro compounds.

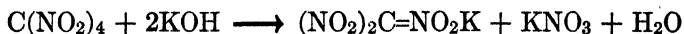
**Hydrolysis.** Primary nitro compounds are hydrolyzed by boiling with hydrochloric acid; the products are hydroxylamine and a carboxylic acid. Since nitroparaffins are now readily available this may become an important synthetic method not only for lower aliphatic acids but also for hydroxylamine.



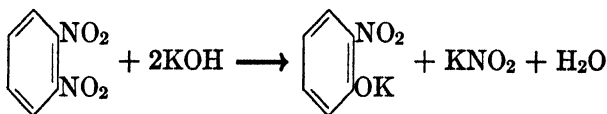
In a similar manner secondary nitro compounds are converted to ketones.



Tertiary nitro compounds in general do not undergo hydrolysis. There are some exceptions, however. Tetranitromethane, for example, is cleaved by concentrated potassium hydroxide to the potassium salts of nitroform and nitric acid.

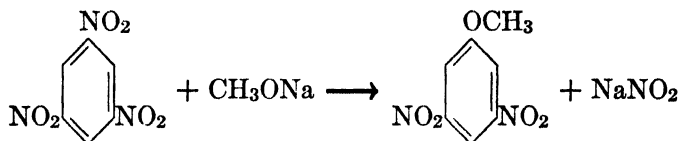


In this connection it is interesting to note that *ortho* and *para* dinitro derivatives of aromatic hydrocarbons also are easily hydrolyzed. In these cases the products are the salts of nitrous acid and the corresponding nitrophenol.



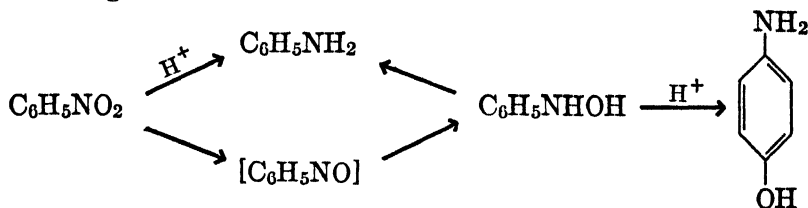
If three nitro groups are present on the benzene ring, one of them can be removed in this way even when they are in *meta* positions with respect

to each other. For example, 1,3,5-trinitrobenzene reacts with sodium methoxide to give 3,5-dinitroanisole.

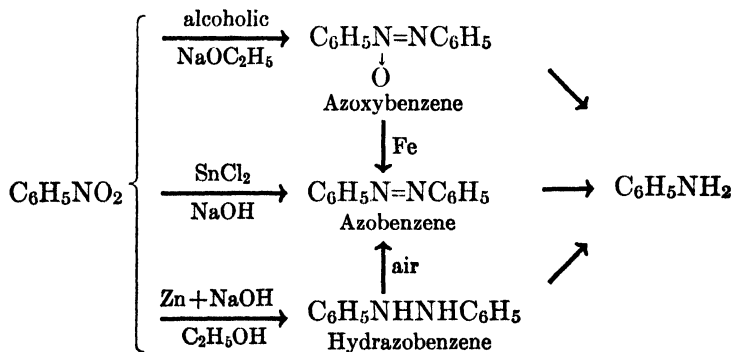


**Reduction.** Nitro compounds of all types are readily reduced to the corresponding primary amines. The reaction has been studied extensively in the aromatic field, where it is most useful, and it has been found that a variety of products may be obtained by suitably altering the conditions.

In acid solution the amine is formed but in neutral media the process can be arrested at an intermediate stage, giving the  $\beta$ -arylhydroxylamine. Presumably the nitroso derivative is formed first. Further reduction gives the amine.



Alkaline reagents give bimolecular reduction products.

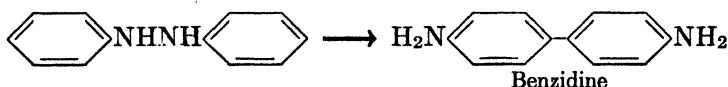


$\beta$ -Phenylhydroxylamine is made by reducing nitrobenzene with zinc dust and water in the presence of ammonium or calcium chloride. Chromic acid oxidizes the hydroxylamine to nitrosobenzene.  $\beta$ -Phenylhydroxylamine also reduces Fehling's solution. This is the basis of a test for the nitro group. The compound is reduced with zinc dust and the reduction product tested with Fehling's solution.

Nitrosobenzene is green in its solutions where it is monomeric but like all nitroso compounds tends to associate to a colorless dimer. It condenses with aniline and  $\beta$ -phenylhydroxylamine to give, respectively, azobenzene and azoxybenzene. This accounts for the formation of the bimolecular products by the reduction of nitrobenzene.

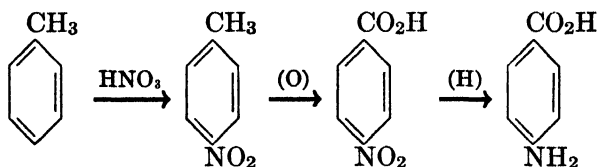
The nitroso group has a higher activating power than the nitro group as seen in the great lability of the bromine atom in *p*-bromonitrosobenzene, and in the ease with which *p*-nitrosoanilines undergo hydrolytic cleavage.

Hydrazobenzene and  $\beta$ -phenylhydroxylamine rearrange in the presence of acids to give benzidine and *p*-aminophenol, respectively.

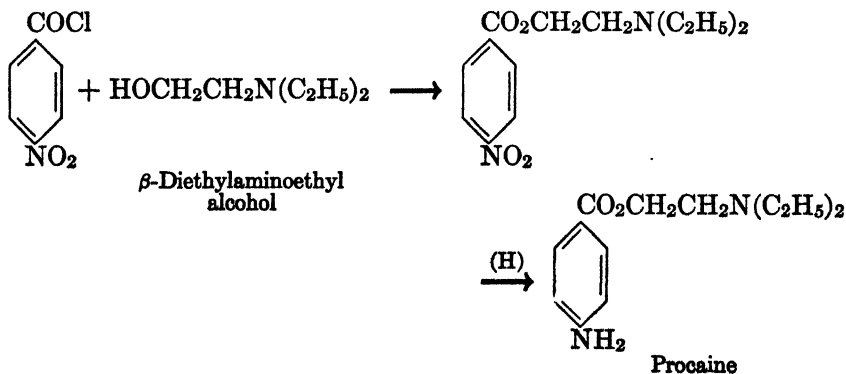


These arrangements are typical of *N*-substituted anilines. The former is known as the benzidine rearrangement.

*p*-Aminobenzoic acid, now recognized as a member of the vitamin B complex, is made by the reduction of *p*-nitrobenzoic acid.

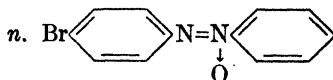
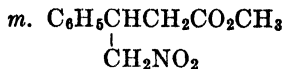
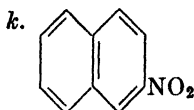
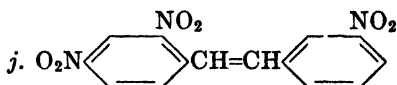
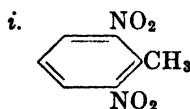
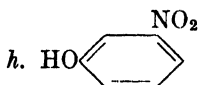
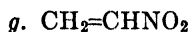
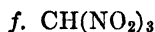
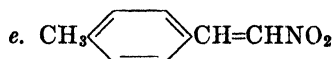
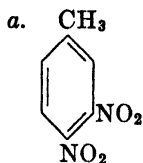


It is interesting that the powerful local anesthetic procaine or novocaine is also derived from this acid. It is made by condensing *p*-nitrobenzoyl chloride with  $\beta$ -diethylaminoethyl alcohol and reducing the resulting ester. In both of these syntheses the starting material is toluene.



## PROBLEMS

1. Outline methods for preparing the following compounds.



2. How do primary, secondary, and tertiary nitro compounds differ in chemical properties?

3. What types of nitro compounds may lose the nitro group by hydrolysis?

4. Outline the reactions which tertiary nitro compounds may undergo with reducing agents.

## SUGGESTED READINGS

HASS, HODGE, and VANDERBILT, "Nitration of Gaseous Paraffins," *Ind. Eng. Chem.*, **28**, 339 (1936).

LIPPINCOTT and HASS, "Action of Mineral Acids on Primary Nitroparaffins," *Ind. Eng. Chem.*, **31**, 118 (1939).

DAVIS, *The Chemistry of Powder and Explosives*, pp. 125-190. John Wiley and Sons, New York, 1941.



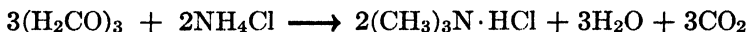
## CHAPTER XXIX

### THE PREPARATION AND PROPERTIES OF AMINES

#### PREPARATION OF AMINES

The Hofmann method of preparing amines by interaction of ammonia and alkyl halides frequently leads to mixtures of primary, secondary, and tertiary amine salts together with quaternary ammonium salts (p. 112). It is, nevertheless, a useful method. In many instances good yields of primary amine can be obtained by using a large excess of ammonia. In some syntheses it is possible to separate the various products, as in the commercial preparation of ethyl-, diethyl-, and triethylamines (p. 113). If a tertiary amine is desired the alkyl halide can be used in slight excess, yielding a mixture of tertiary amine salt and quaternary ammonium salt; the latter can be decomposed to the tertiary amine and alkyl halide by heating *in vacuo*.

Alkylating agents other than alkyl halides can be used. For example, formaldehyde can be converted to methylamine or trimethylamine by heating formalin or paraformaldehyde with ammonium chloride.

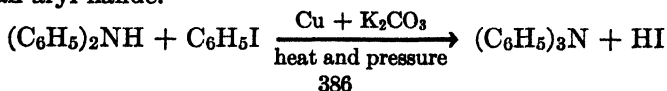


Even alcohols can be used instead of alkyl halides if the reaction is carried out under high pressure in the presence of a copper chromite catalyst. Methylamine is made in a similar way.



Dimethyl- and trimethylamines are also formed, but by using an excess of ammonia methylamine can be obtained in about 80 per cent yield.

As a laboratory procedure the reaction of halides is limited practically to primary alkyl halides, isopropyl bromide, and compounds, such as  $\alpha$ -halo acids and 2,4-dinitrochlorobenzene, in which the halogen is activated. However, the commercial preparation of aniline from chlorobenzene (p. 114) is an adaptation of the Hofmann process. The commercial preparation of triphenylamine is another example involving the use of an aryl halide.

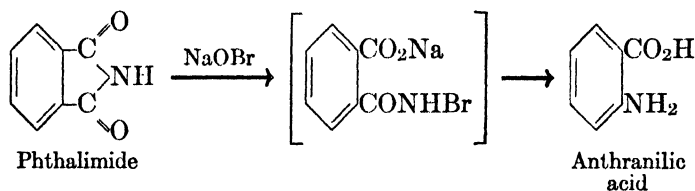


When alkyl halides are used the rate of reaction is greatly influenced by the solvent employed. For example, isopropyl bromide and diethylamine react very slowly without a solvent but rapidly in ethylene glycol or glycerol.

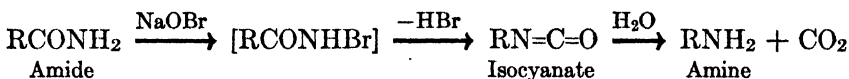
### The Preparation of Pure Primary Amines

Pure primary amines are usually made by special methods. Some of these will now be presented.

**Hofmann's Hypobromite Method.** Amides react with bromine or chlorine in alkalis, i.e., with hypohalites, to give amines with one less carbon atom. Anthranilic acid has been prepared commercially in this way.



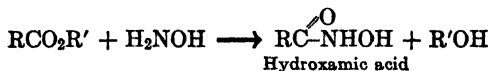
The reaction is characteristic of amides and is known as the Hofmann hypobromite synthesis of amines. An isocyanate is formed as an intermediate. It should be noticed that the isocyanate is formed by a molecular rearrangement since the alkyl group has moved from a carbon atom to a nitrogen atom.



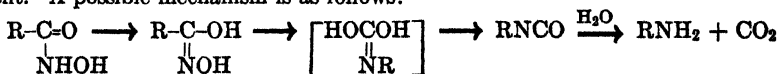
Sometimes interaction of the isocyanate and free amine produces disubstituted ureas. Also, if the amine comes in contact with excess hypohalite, it is oxidized to the corresponding nitrile.

**The Curtius Method.\*** Acid azides also decompose to give primary amines.

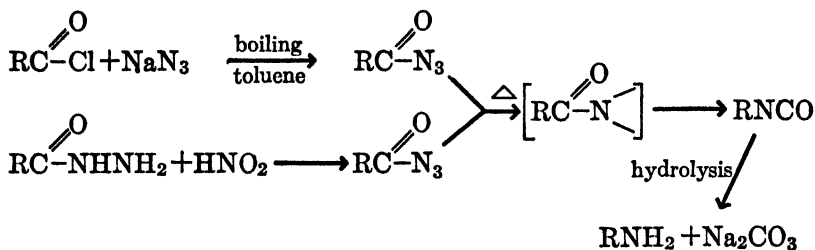
\* The Hofmann and Curtius rearrangements are similar to the Lossen rearrangement. The latter is characteristic of hydroxamic acids. These acids are formed when an ester, amide, or anhydride reacts with hydroxylamine.



Thermal decomposition of hydroxamic acids is accompanied by the Lossen rearrangement. A possible mechanism is as follows:

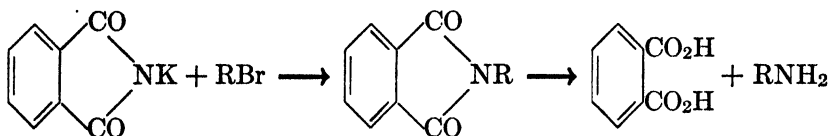


This mechanism recalls that postulated for the Beckmann rearrangement.

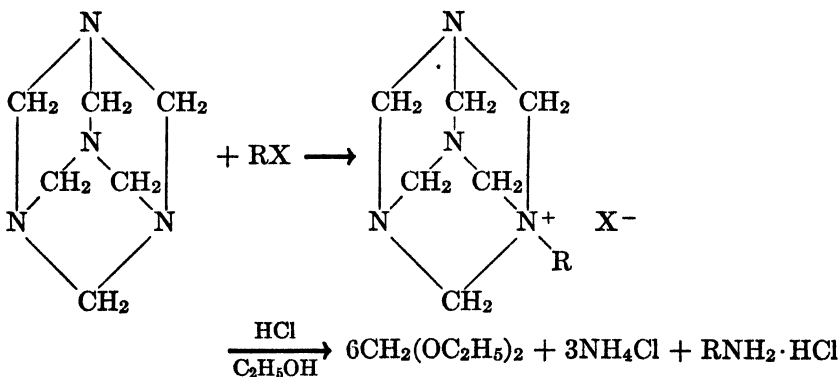


This resembles Hofmann's method very closely. Both are good, but the Hofmann procedure is more often used because of the availability of the reagents.

**Gabriel's Phthalimide Method.** The use of this method in the synthesis of *dl* glutamic acid already has been mentioned (p. 338). It is generally useful with halogen compounds which are sufficiently reactive.



**Delépine's Method.** Delépine found that hexamethylenetetramine will react with an alkyl halide to form a quaternary ammonium salt which can be hydrolyzed to a primary amine.

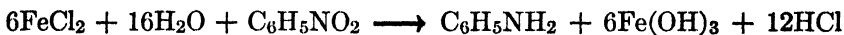
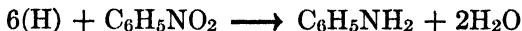


This method is satisfactory only for amines that boil high enough to be separated easily from ammonia.

**The Use of Chloroamine.** Primary amines of the type  $\text{R}_3\text{CNH}_2$  are very difficult to synthesize. One of the best ways to make them is by operating upon chloroamine with the appropriate Grignard reagent.



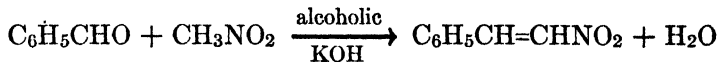
**Reduction Methods.** The reduction of nitro compounds is the standard method for making aromatic amines. It has been discussed in connection with nitro compounds. The commercial method for reducing nitrobenzene to aniline involves the use of iron and water with a trace of acid. The process may be represented by the following equations:



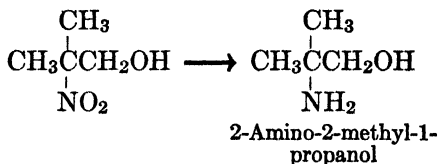
The net result, expressed as follows, shows that the acid acts merely as a catalyst:



Aliphatic amines occasionally are made by this method.  $\beta$ -Phenylethylamine, for example, is formed by the reduction of  $\beta$ -nitrostyrene. The latter, as was pointed out earlier (p. 380), is a condensation product of benzaldehyde and nitromethane.

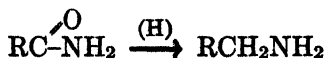
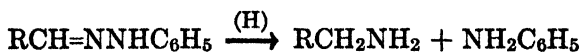
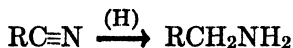
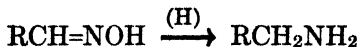


Methylol derivatives of aliphatic nitro compounds (p. 380) are converted by hydrogenation into amino alcohols. 2-Amino-2-methyl-1-propanol, for example, is made in this way.

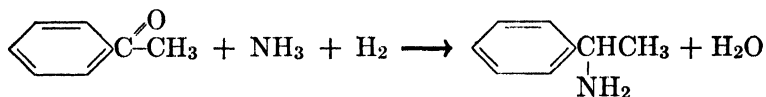


Aliphatic amino alcohols of this type are used as emulsifying agents.

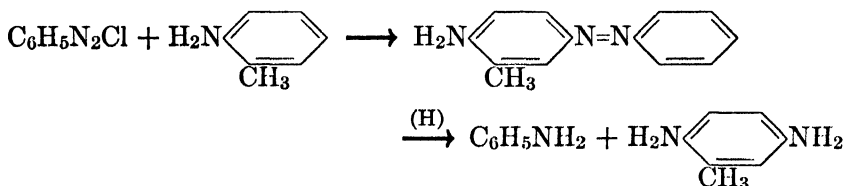
Oximes, nitriles, hydrazones, and amides can be reduced catalytically or with sodium and absolute alcohol to give primary amines. In the latter method no water must be present as hydrolysis will occur. Acid reduction is also complicated by hydrolysis.



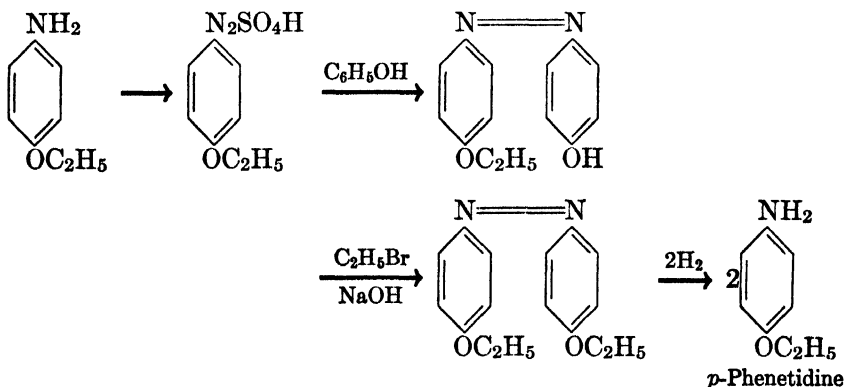
A more convenient method for transforming aldehydes and ketones to amines consists in hydrogenating the carbonyl compound in the presence of an excess of ammonia. Nickel is used as the catalyst.  $\alpha$ -Phenylethylamine is prepared in this way.



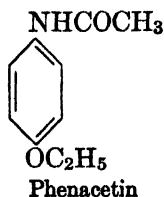
The reduction of azo compounds with sodium hydrosulfite ( $\text{Na}_2\text{S}_2\text{O}_4$ ) has been important in determining the structure of azo dyes. It can be used as a method of preparing amines, simply by coupling diazotized aniline at the desired position and reducing the product so formed.



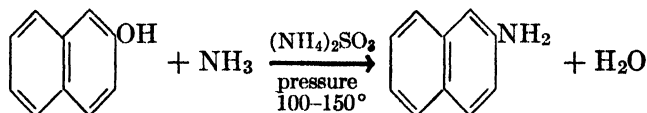
An elegant synthesis of *p*-phenetidine is based on this reaction. The product is one of the raw materials; the process uses primarily phenol and ethyl bromide.



This was an important part of a synthesis of the antipyretic phenacetin.



**Special Methods.** The Bucherer process is excellent for preparing  $\beta$ -naphthylamine.



This reaction is reversible; by heating a naphthylamine with aqueous sodium bisulfite a naphthol can be obtained. The process is of value in the preparation of many substituted naphthols and naphthylamines but is of very little use in the synthesis of phenols and anilines. Another method of converting naphthols to naphthylamines consists in heating the former with a zinc chloride-ammonia complex at  $300^\circ$ .

Allylamine is prepared by hydrolysis of allyl isothiocyanate, the mustard oil present in black mustard.

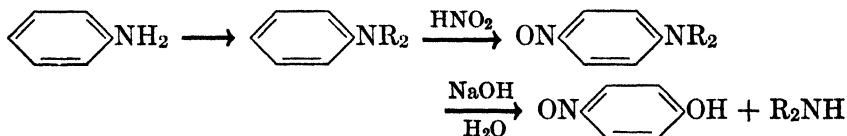


This is a general method for making amines but is useful only in a very few cases in which the isothiocyanate can be made from the corresponding alkyl halide. Allyl and benzyl isothiocyanates are two examples. When benzyl or allyl thiocyanate is distilled it rearranges to the more stable isomer.

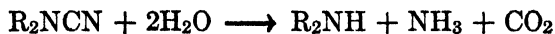


### Secondary Amines

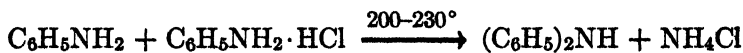
**Hydrolysis of *p*-Nitroso Disubstituted Anilines.** For secondary amines of low molecular weight the hydrolysis of *p*-nitroso disubstituted anilines is a good method.



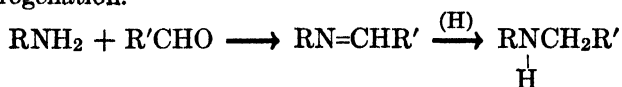
**Hydrolysis of Disubstituted Cyanamides.** This method is used in preparing diethylamine and di-*n*-butylamine, which are employed in the synthesis of certain drugs.



**Heating a Primary Amine with Its Hydrochloride.** This is the commercial method for preparing diphenylamine.

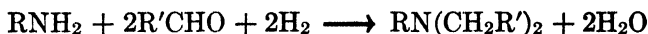


**Reduction of a Schiff Base.** Secondary amines can be obtained by the reduction of Schiff bases with sodium and alcohol or by means of catalytic hydrogenation.



### Tertiary Amines

**Reduction of Carbonyl Compounds in the Presence of Ammonia or Amines.** Ammonia, or primary or secondary amines, when treated with aldehydes or ketones in a reducing medium, give tertiary amines.



Catalytic hydrogen, formic acid, or metal and acid can be used as the reducing agent. The method is good for nearly all low molecular weight amines but is not satisfactory for the preparation of tertiary aromatic amines from primary aromatic amines.

**Alkylation of Amines.** Methyl sulfate reacts with primary amines to give the corresponding tertiary amines.



Alcohols under high pressure in the presence of a copper chromium oxide catalyst also serve as alkylating agents.



### REACTIONS OF AMINES

**Salt Formation.** Most amines tend to form salts with acids. This tendency can be increased or diminished by the presence in the molecule of other groups. In commenting on the basicity of amines, it is convenient to include other nitrogen compounds such as nitriles, amides, oximes, imides, sulfonamides, and hydrazines, all of which can be considered as derivatives of ammonia.

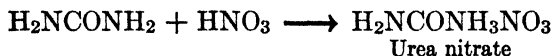
When the hydrogen atoms of ammonia are replaced by aliphatic radicals such as methyl and ethyl, there is an increase in the basic properties of the nitrogen atom. The apparent basic dissociation constants of methylamine and ammonia in water are  $5 \times 10^{-4}$  and  $2 \times 10^{-5}$ , respectively. A separation of ammonia and methylamine is based on this difference. When a mixture of the two is treated with an insufficient amount of hydrogen chloride the amine is neutralized preferentially and the ammonia is left free.

On the other hand, replacement of a hydrogen atom of ammonia with an aryl radical decreases the basicity of the nitrogen. Aniline is a very weak base. Its apparent basic dissociation constant is  $3 \times 10^{-10}$ . Its

hydrochloride can be dissolved in water and titrated with standard alkali, using phenolphthalein as an indicator. Certain groups in the ring diminish even further the basicity of aniline; nitro groups, halogens, and other negative substituents act in this way. If two of the hydrogens of ammonia are replaced by aryl groups, the compound formed is essentially neutral. Diphenylamine forms salts with concentrated sulfuric acid or with dry hydrogen chloride in benzene solution. In water these salts are hydrolyzed to the free amine. Three phenyl (or aryl) groups attached to a nitrogen atom remove basic properties.

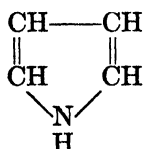
When a methyl group is attached to the nitrogen atom in aniline, the basicity is increased. Methylaniline and dimethylaniline are stronger bases than aniline. Ring nitrogen compounds such as quinoline and pyridine are very much like aryl amines such as dimethylaniline.

If one replaces a hydrogen atom of ammonia with an acyl group to form an amide, a neutral compound results. Thus one acyl group has about the same effect as two aryl groups. Urea resembles a monobasic amine; nitric acid converts it to urea nitrate (p. 125).

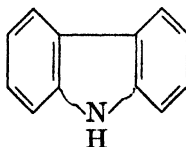


If two acyl groups are introduced in place of two hydrogen atoms of ammonia, the resulting imide is acidic rather than basic. Imides form salts with aqueous alkalis. One sulfonyl group seems to be approximately equal in effect to two acyl groups because the sulfonyl derivatives of primary amines are alkali-soluble.

In pyrrole and carbazole the basicity of the nitrogen is very low and the tendency to act as an acid appears. These compounds resemble acid imides in their ability to form salts with potassium hydroxide.

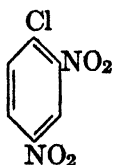


Pyrrole

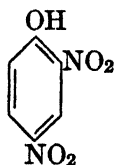


Carbazole

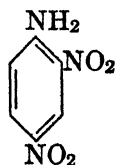
The basicity of aniline is greatly diminished by the introduction of nitro or other *m*-directing groups in the *ortho* or *para* positions. This is another manifestation of the influence of such groups.



Halogen active



Strongly acid



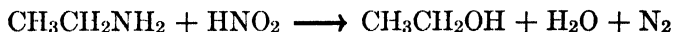
Neutral



Certain amides such as *N*-ethylacetanilide exhibit pronounced basic properties. This may prove to be characteristic of tertiary amides.

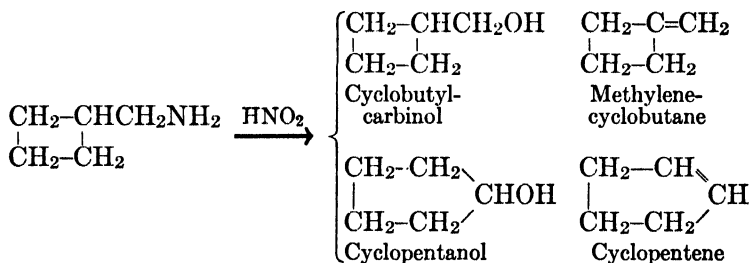
These rules seem to be quite general and are very useful in predicting the properties of new compounds. They help a great deal in qualitative organic analysis.

**Reactions with Nitrous Acid.** Probably the most important reaction of amines is that with nitrous acid. In the aliphatic series, primary amines give alcohols when treated with nitrous acid.



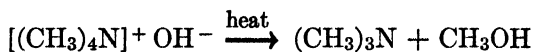
Higher amines always yield also isomeric alcohols formed by molecular rearrangement (p. 118); olefins also are found among the products. Methylamine does not yield methanol.

This reaction has been used to bring about ring enlargement. For example, cyclobutylmethylamine yields some cyclopentanol and cyclopentene along with cyclobutylcarbinol and methylenecyclobutane.

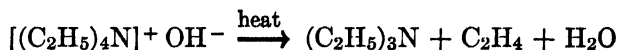


This type of rearrangement is frequently encountered and is known as the Demjanow rearrangement.

**Pyrolysis of Quaternary Ammonium Bases.** The pyrolysis of quaternary ammonium bases is of interest from a number of points of view. In the first place, it is a means of obtaining tertiary amines from the Hofmann reaction.

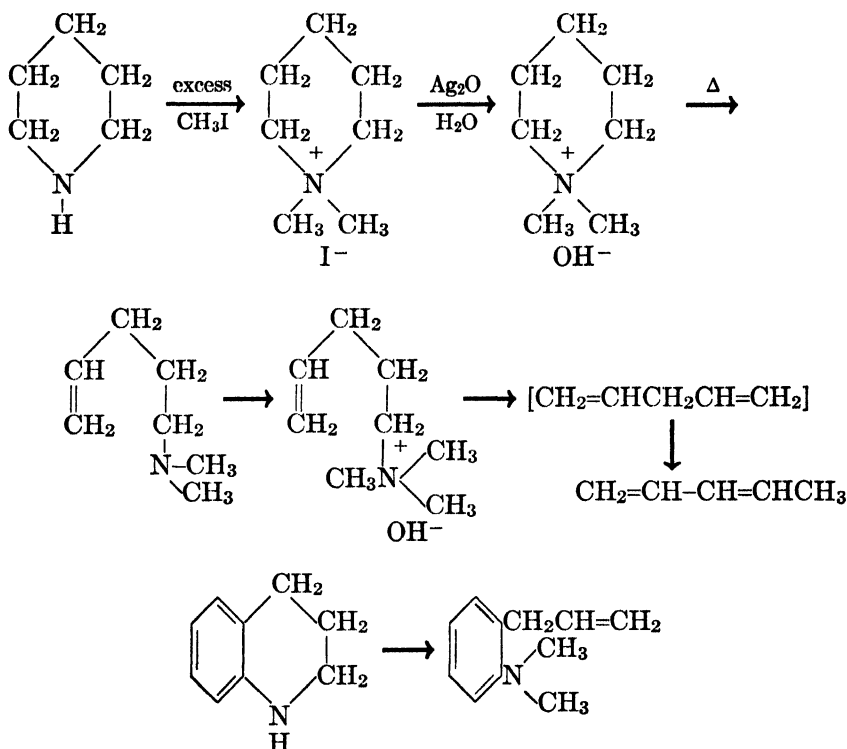


With more than one carbon atom in the alkyl group, an olefin occurs as a product rather than an alcohol.



Hofmann has applied this in a method for determining the structure of an organic compound, as well as for the removal of a nitrogen atom from the molecule, the opening of a nitrogen ring, and the preparation of

certain types of unsaturated compounds. This exhaustive methylation procedure is made clear by typical cases.

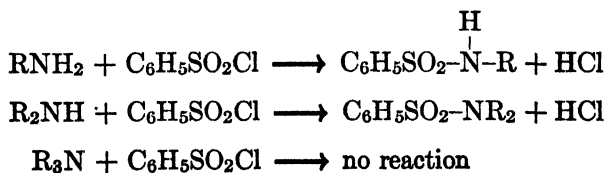


This degradation method is fairly general and useful.

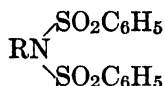
**Separation of Mixtures of Amines.** Ever since Hofmann found that he could get a mixture of amines by treating ammonia with an alkyl halide, the problem of the separation of amines has occupied the attention of chemists.

1. *Fractional distillation* is still the best method.

2. *Hinsberg* devised a procedure using benzenesulfonyl chloride. After the amines have been steam-distilled from the basic solution of the ammonium salts, the distillate is made alkaline and benzenesulfonyl chloride is added. The products obtained are as follows:

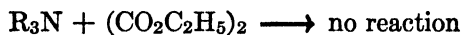
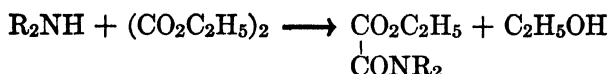
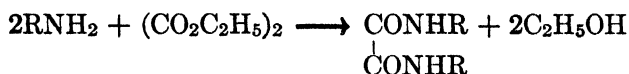


The three substances are separable because the primary amine derivative is alkali-soluble, the unchanged tertiary amine is acid-soluble, and the secondary amine derivative insoluble in both acid and base. This method is not very satisfactory in the laboratory, particularly since primary amines usually form some of the neutral dibenzenesulfonyl derivative.



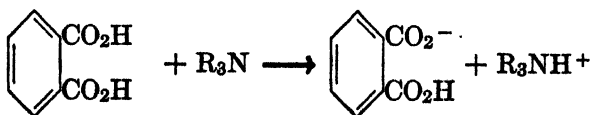
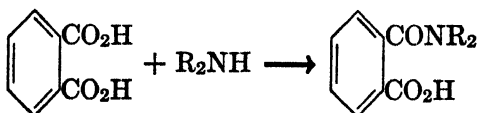
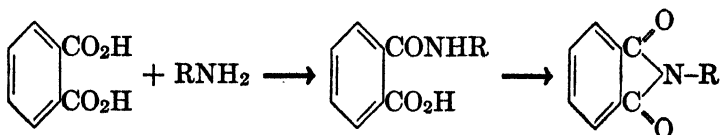
The Hinsberg method is of greater value in classifying unknown amines than in separating mixtures.

3. Another method of separation employs *ethyl oxalate*. When it is heated with a mixture of amines the following reactions take place:



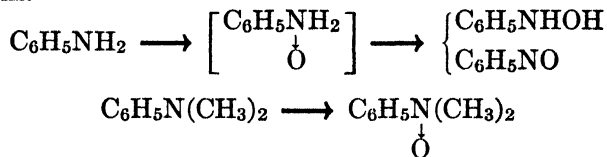
The primary derivative is a high-melting crystalline solid, whereas the secondary is an oil. The three products can be separated by their solubility behavior. This method of separation is complicated by the fact that the higher primary amines tend to stop at the monoamide stage.

4. *Phthalic acid* has also been used to separate amines. On heating, the primary and secondary amines react to form amides while the tertiary does not. These amides are alkali-soluble. On further heating the primary amide forms an imide which is not alkali- or acid-soluble.



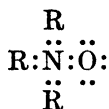
**Oxidation of Amines.** Amines are readily oxidized but such reactions possess little preparative value. Reagents for this purpose fall into two classes. The first is exemplified by Caro's acid (monopersulfuric acid,  $\text{H}_2\text{SO}_5$ ) which adds an oxygen atom to the nitrogen atom of the amine. With the second type, which includes nearly all the ordinary oxidizing agents, the removal of hydrogen is the first step of the oxidation.

The oxidation of aniline and dimethylaniline by Caro's acid are illustrations.



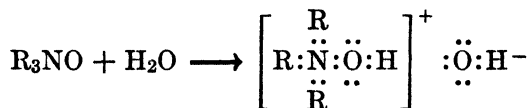
In general, tertiary amines react with Caro's acid to give amine oxides.

The interest in the amine oxides comes chiefly in connection with the valence of nitrogen. The formula is written as follows:

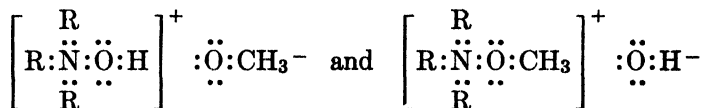


The oxygen atom is held by a coordinate covalence.

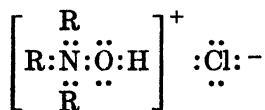
Just as amines combine with water to form ammonium bases, amine oxides take up water to form bases.



One hydroxyl group is held by a covalence, the other by an electrovalence. The difference between the two is definite and has been shown by the synthesis of the following two isomeric compounds:

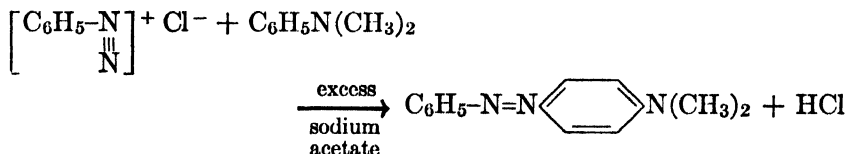


In the positive ion there is no difference between the four covalences except as to the original source of the electrons. These amine oxide bases react with acids to form salts just as the ammonium bases do.

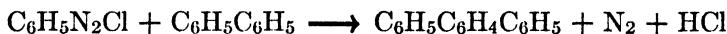
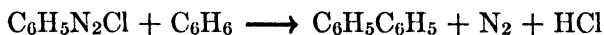




as OH, CN, and Cl. In basic solution the diazotate reacts. Coupling reactions are carried out in basic or faintly acidic solutions.

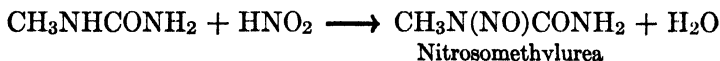


Replacement of the diazonium group by aryl radicals is brought about by decomposing the salt in the presence of a hydrocarbon such as benzene. The reaction is catalyzed by aluminum chloride or better by copper. In the latter case not only biphenyl but also terphenyl, quaterphenyl, and quinquephenyl are formed.

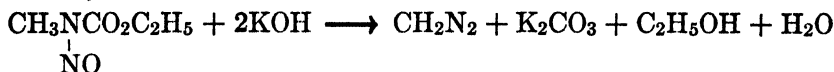
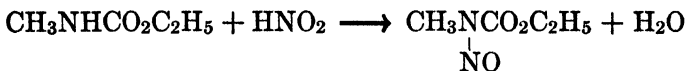
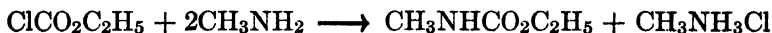


A continuation of this process is evidently responsible for the formation of the higher hydrocarbons.

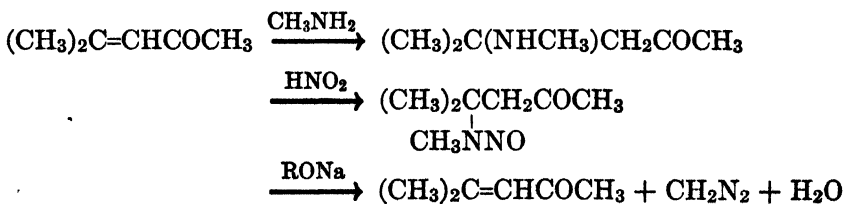
**Diazomethane.** This useful reagent is prepared by the following sequence of reactions:



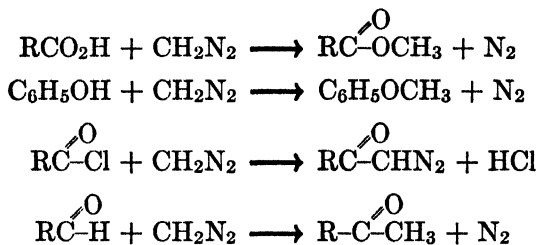
It can also be made from nitrosomethylurethan.



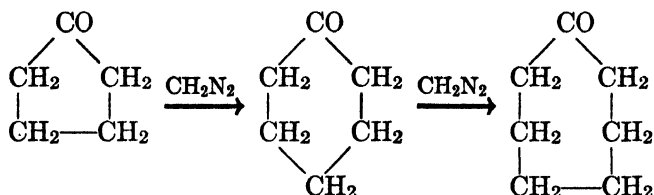
A third preparation utilizes methylamine, mesityl oxide, and nitrous acid.



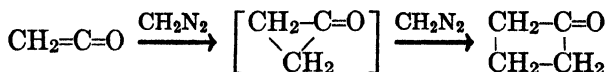
Diazomethane is a very poisonous yellow gas; it is generally used in ether solutions. It is a very effective methylating agent for acids, phenols, enols, and imides but does not ordinarily attack alcohols or amines. Its most important reactions are illustrated below.



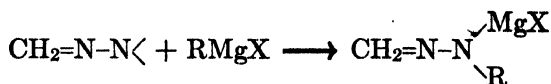
A cyclic ketone when treated with diazomethane yields the next higher cyclanone. Thus cyclopentanone and cyclohexanone yield, respectively, cyclohexanone and cycloheptanone.



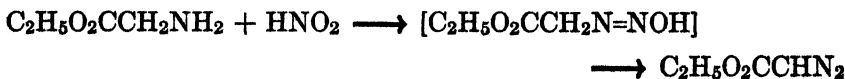
In an attempt to use this method in the preparation of cyclopropanone by treating ketene with diazomethane it was observed that the chief product was cyclobutanone; presumably cyclopropanone was an intermediate.



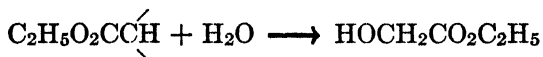
Of great interest is the reaction of diazomethane with the Grignard reagent. It does not behave like ketene or isocyanates but adds both the R and the MgX to the terminal nitrogen atom.



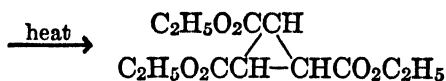
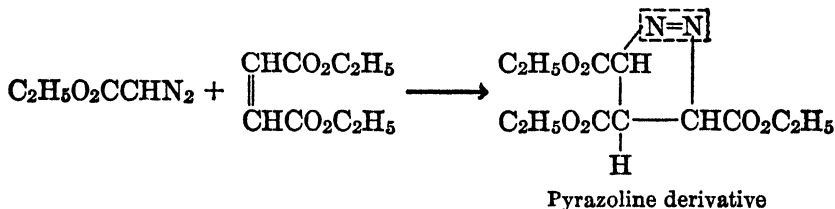
**Diazoacetic Ester.** Although diazomethane must be prepared indirectly, aliphatic amines can be converted to diazo compounds if the amino group is *alpha* to a carbonyl group. Diazoacetic ester, for example, is prepared from the ethyl ester of glycine.



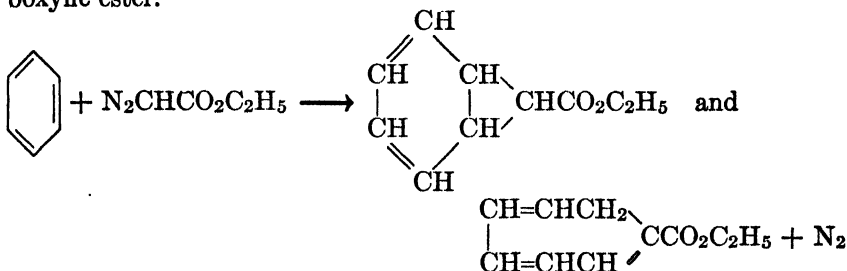
Most of the reactions of this compound appear to be those of the  $\text{C}_2\text{H}_5\text{O}_2\text{CCH}\cdot$  radical. Hydrogen ion or heat causes the loss of nitrogen and the radical so formed dimerizes or reacts with other molecules which may be present.



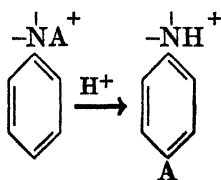
It gives similar reactions with hydrogen chloride, iodine, acids, aldehydes, etc. With unsaturated compounds nitrogen is not lost; cyclic compounds are formed which do lose nitrogen on heating.



Diazoacetic ester reacts with benzene at  $130^\circ$  to form norcaradiene-carboxylic ester and its rearrangement product, cycloheptatrienecarboxylic ester.



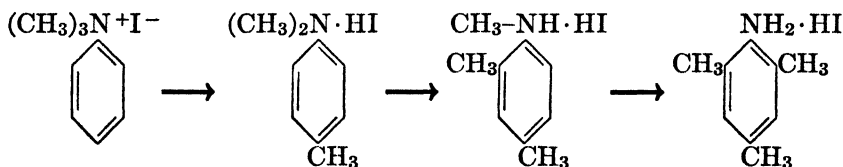
**Rearrangement.** The rearrangement of certain *N*-substituted anilines has already been mentioned. This is a rather general phenomenon and may be summarized by the following transformation where A equals halogen, alkyl, hydroxyl, amino, nitroso, nitro, etc.





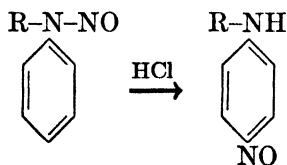
In all cases the nitrogen atom must be in the tetravalent condition.

By heating trimethylphenylammonium iodide at temperatures from 250 to 335° the ring may be methylated progressively.

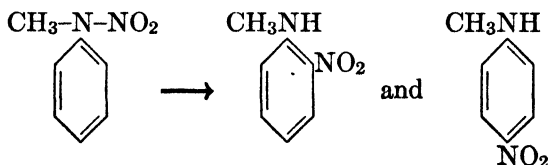


This is known as the Hofmann rearrangement.

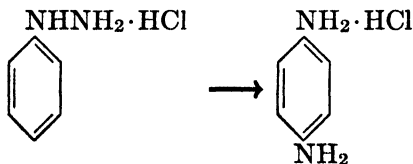
Nitrosoamines undergo a similar change known as the Fischer-Hepp rearrangement.



Similarly phenylnitroamines yield nitroanilines.



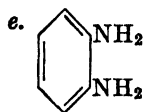
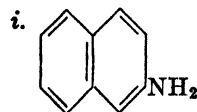
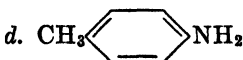
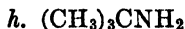
The rearrangement of phenylhydrazine hydrochloride at 200° is another example.



The benzidine rearrangement, mentioned earlier, is of this type.

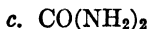
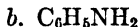
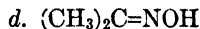
## PROBLEMS

1. Give useful methods for making the following amines:



2. Discuss the behavior of the various types of amines toward (a) nitrous acid, (b) benzenesulfonyl chloride, (c) phthalic acid.

3. Arrange the following compounds in an order of increasing basic strength.



## SUGGESTED READINGS

SIDGWICK, *Organic Chemistry of Nitrogen*, Chapters II and III, Clarendon Press, Oxford, 1937.

FRANKLIN, "The Hofmann-Beckmann-Curtius-Lossen Rearrangements," *Chem. Rev.*, **14**, 219 (1934).

SAUNDERS, *The Aromatic Diazo Compounds*, Edward Arnold and Company, London 1936.

SMITH, "Aliphatic Diazo Compounds, Nitrones, and Structurally Analogous Compounds," *Chem. Rev.*, **23**, 193 (1938).

## CHAPTER XXX

### ORGANIC SULFUR COMPOUNDS

One of the early efforts to classify organic compounds containing oxygen and nitrogen was to regard them as substitution products, respectively, of water and ammonia. Thus ethers are obtained by putting alkyl or aryl groups in place of the two hydrogen atoms of water, and amines by replacing similarly one or more of the hydrogen atoms of ammonia. By analogy sulfur compounds might be regarded as derivatives of hydrogen sulfide. Those having one radical are mercaptans (p. 61) or thiophenols, those with two are thio ethers (p. 62)|

$\text{RSH}$   
Mercaptan

$\text{ArSH}$   
Thiophenol

$\text{RSR}$   
Thio ether

Disulfides are also known (p. 62) but these show only a formal resemblance to peroxides.

$\text{R-S-S-R}$   
Disulfide

$\text{R-O-O-R}$   
Peroxide

In general, the analogies between sulfur and oxygen compounds are of a structural rather than a chemical nature.

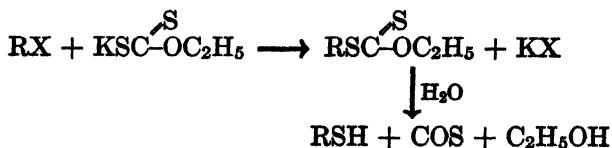
The more important sulfur compounds are those in which the sulfur atom shows a valence higher than two, and these are very different from any known compounds of oxygen. The sulfonic acids are the most important examples.

#### Mercaptans

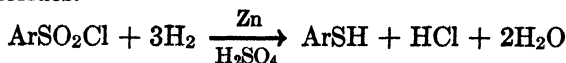
These substances are made by the interaction of alkyl halides and the mono sodium salt of hydrogen sulfide (p. 61).



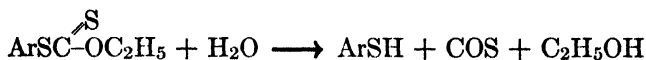
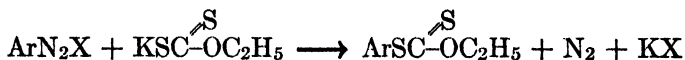
Another method involves the use of potassium xanthate.



In the aromatic series the thiophenols are obtained by reduction of the sulfonyl chlorides.



Thiophenols can also be made from diazonium salts by replacement.



Mercaptans differ from alcohols in being much less associated. The following table of boiling points shows this difference:

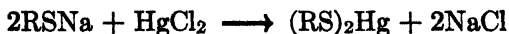
TABLE XXXII

MERCAPTANS AND ALCOHOLS

	Boiling Point		Boiling Point
$\text{H}_2\text{S}$	$-61^\circ$	$\text{H}_2\text{O}$	$+100^\circ$
$\text{CH}_3\text{SH}$	6	$\text{CH}_3\text{OH}$	65
$\text{C}_2\text{H}_5\text{SH}$	37	$\text{C}_2\text{H}_5\text{OH}$	78
$n\text{-C}_3\text{H}_7\text{SH}$	68	$n\text{-C}_3\text{H}_7\text{OH}$	97
$n\text{-C}_4\text{H}_9\text{SH}$	98	$n\text{-C}_4\text{H}_9\text{OH}$	117

The most characteristic property of the mercaptans and thiophenols is their intensely disagreeable odor. It is said that 1/460,000,000 mg. of ethyl mercaptan can be detected by its odor. This is 1/250 of the smallest amount of sodium which can be detected spectroscopically. The unpleasant odor of crude petroleum is due primarily to mercaptans. *n*-Butyl mercaptan is a constituent of the secretion of the skunk.

Mercaptans and thiophenols are also more acidic than the corresponding oxygen compounds. This could be predicted from the fact that they are monosubstituted derivatives of hydrogen sulfide, which is an acid. A characteristic property of mercaptans is the ease with which their salts form mercury derivatives.



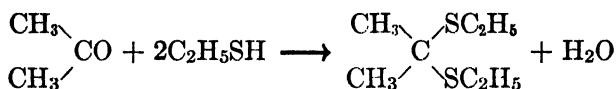
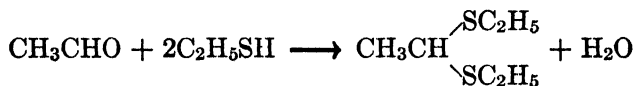
The name mercaptan (*corpus mercurium captans*) comes from this fact

Mercaptans react with acids to form esters.



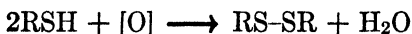
This indicates that in esterification, in general, the hydroxyl group comes from the acid rather than the alcohol.

Mercaptans form mercaptals with aldehydes and mercaptoles with ketones. Acetaldehyde and acetone may be cited as illustrations.

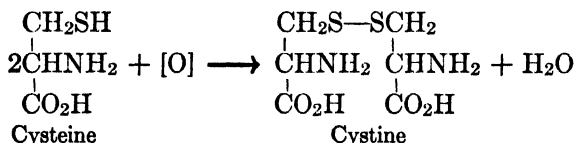


The latter equation represents one step in the process used to manufacture sulfonal (p. 78).

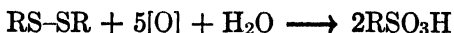
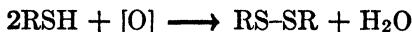
The most interesting reaction of mercaptans is the conversion to disulfides by oxidation (p. 62).



The formation of cystine from cysteine is an example.



The disulfides are probably formed as intermediates in the oxidation of mercaptans to sulfonic acids (p. 62).



It will be noted that this behavior is very different from that of alcohols, which undergo oxidation at the  $\alpha$ -carbon atom.

### Thio Ethers

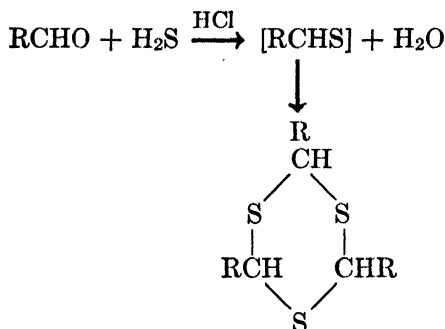
Thio ethers (p. 62) are prepared by the interaction of mercaptides and alkyl halides.



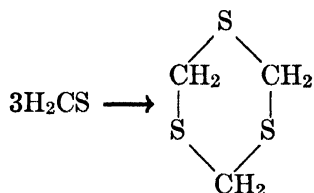
They may also be made by treating alkyl halides with alkali sulfides.



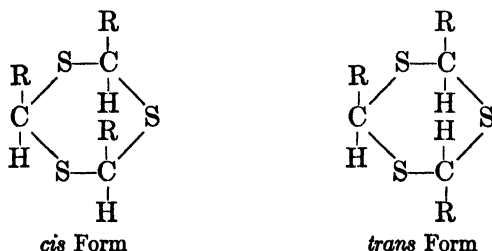
*sym.*-Trithianes, compounds closely related to thio ethers, are formed by the treatment of aldehydes or ketones with hydrogen sulfide in the presence of hydrochloric acid. Thioaldehydes and thioketones are presumably intermediates in this reaction.



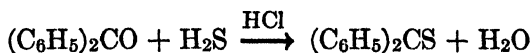
These substances are analogous to paraldehydes. The parent compound, *sym.*-trithiane, is a trimer of thioformaldehyde.



The trithianes from higher aldehydes exist in *cis* and *trans* modifications.

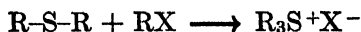


Recently *thioketones* have been prepared in the monomeric forms. Benzophenone is converted to thiobenzophenone by treatment with hydrogen sulfide and hydrogen chloride.

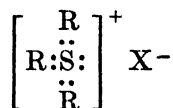


It is a deep blue solid, melting at  $52^\circ$ . Thiocamphor can be made by a similar method.

Thio ethers react with alkyl halides to give sulfonium halides in which the sulfur atom is trivalent.

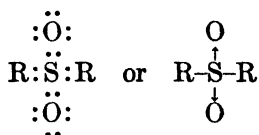
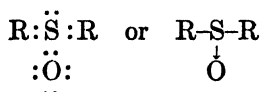


These compounds have the following electronic structure:

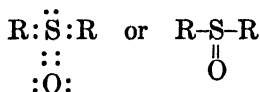


### Sulfoxides and Sulfones

Thio ethers may be oxidized to sulfoxides and sulfones (p. 63). These interesting substances have been found to have the following structures:



In the sulfoxides the sulfur atom is trivalent and in the sulfones tetravalent. It is possible to write the sulfoxides as unsaturated compounds but this would give ten valence electrons to the sulfur atom.

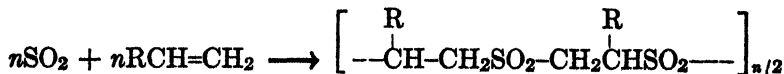


An interesting proof of the accepted structure for sulfoxides is the fact that the dithiane disulfoxide exists in *cis* and *trans* modifications (p. 221).

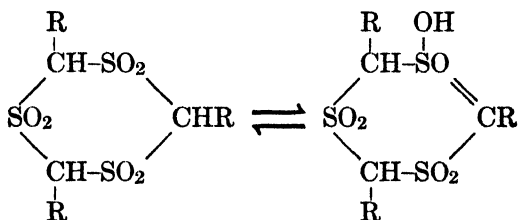
Sulfones may be obtained by the oxidation of thio ethers or sulfoxides. Aromatic sulfones can be made by the action of sulfuric acids on aromatic hydrocarbons.



Sulfur dioxide reacts with olefins to give polysulfones.

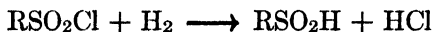


Trisulfones from certain trithianes are acidic and form sodium salts. It is not known whether this is due to enolization; if so, it requires the assumption of an expanded valence shell for sulfur.



### Sulfinic Acids

These have been studied mostly in the aromatic series. They are made by reducing sulfonyl chlorides with zinc and alkali or with sodium sulfite.



They have also been prepared by the action of sulfur dioxide on the Grignard reagent (p. 270).

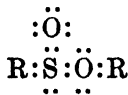


They have the structure  $\text{R}:\ddot{\text{S}}:\ddot{\text{O}}:\text{H}$  or  $\text{RS} \begin{array}{c} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ . The alternative for-

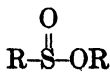
mula  $\text{R}:\ddot{\text{S}}:\ddot{\text{O}}:$  or  $\text{RS} \begin{array}{c} \nearrow \text{O} \\ \searrow \text{H} \end{array}$  also satisfies the requirements of the valence

theory and many of the reactions seem to be best explained by this struc-

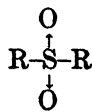
ture. However, the esters must have the structure  $\text{R-S} \begin{array}{c} \nearrow \text{O} \\ \searrow \text{OR}' \end{array}$  for they are resolvable. As was pointed out earlier, only the form *a* in which sulfur is trivalent will permit this. Forms *b* and *c* are excluded.



(a)



(b)



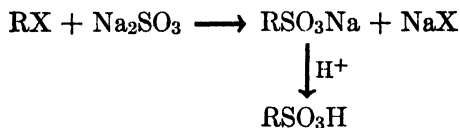
(c)

### Sulfonic Acids

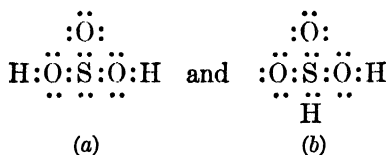
The sulfonic acids of the aromatic series are of great importance. Aliphatic sulfonic acids are also known, however. These can be



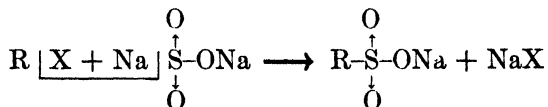
prepared by the oxidation of mercaptans (p. 62) or by the action of sodium sulfite on an alkyl halide.



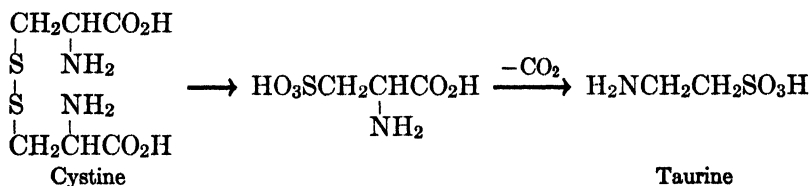
The latter reaction recalls the fact that sulfurous acid may be written in isomeric forms.



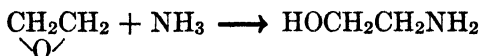
The reaction in question may be explained by assuming form *b* for the sodium salt.



The most interesting sulfonic acid of the aliphatic group is taurine. It occurs in the bile of animals and is thought to be a degradation product of cystine.

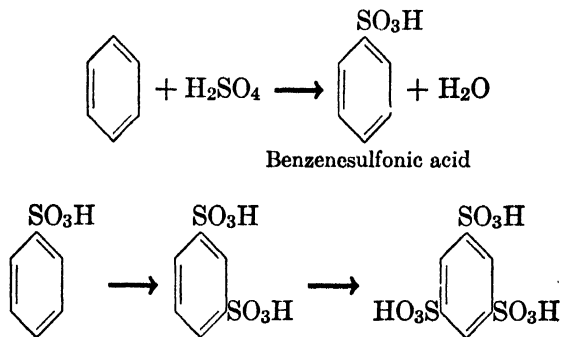


It can be synthesized by the following sequence of reactions:



Aromatic sulfonic acids frequently are used as intermediates in the synthesis of other substances; also, the sulfonic acid group may be introduced to increase the water solubility of a molecule. Aryl sulfonic

acids and most of their sodium salts are water-soluble. These substances usually are made by direct sulfonation of aromatic compounds. The sulfonation of benzene will serve as an example. Mono-, di-, and trisubstituted derivatives are obtained.



Commercially, benzenesulfonic acid is isolated as the sodium salt. This separation depends on the fact that the calcium sulfonates are soluble in water. The process is known as *liming out* and consists in neutralizing the sulfonation mixture (after dilution with water) with lime. The insoluble calcium sulfate is separated by filtration and the calcium sulfonate remains in the filtrate. Addition of sodium carbonate converts it to the sodium salt which is obtained by evaporating the solution to dryness.



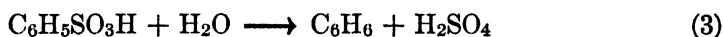
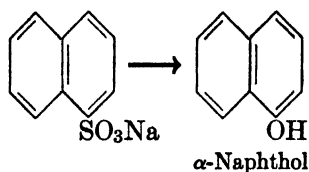
Another method of obtaining sodium sulfonates is to treat the sulfonation mixture with sodium chloride. The sodium sulfonate precipitates because it is insoluble in brine.



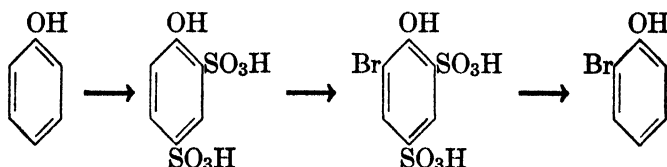
The free sulfonic acids are rarely prepared. They are obtained by treating the calcium, barium, or lead salts with the calculated amount of sulfuric acid, removing the insoluble sulfate, and concentrating the aqueous solution.

The sulfonic acids are solids and generally crystallize as hydrates. Some are hygroscopic. Benzenesulfonic and *p*-toluenesulfonic acids are sometimes used as catalysts where a strong nonvolatile acid is required. Sulfonic acids resemble mineral acids in strength.

**Replacement of the  $\text{SO}_3\text{H}$  Group.** The sulfonic acid group may be replaced by hydroxyl, cyano, or hydrogen. All these reactions furnish important synthetic methods.



Reaction 3 takes place when the sulfonic acid is heated with water above  $100^\circ$  under pressure. An example of its use is met in the synthesis of *o*-bromophenol. Phenol is sulfonated to block the *para* and one *ortho* position and after the bromination has been effected the reaction mixture is subjected to steam distillation. The sulfonic acid groups are removed and *o*-bromophenol passes over with the steam.



### Derivatives of Sulfonic Acids

Sulfonic acids are converted to the corresponding chlorides by phosphorus pentachloride or oxychloride.



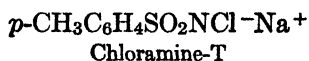
The preparation of aromatic sulfonyl chlorides is best accomplished by treating the aromatic compound with chlorosulfonic acid.



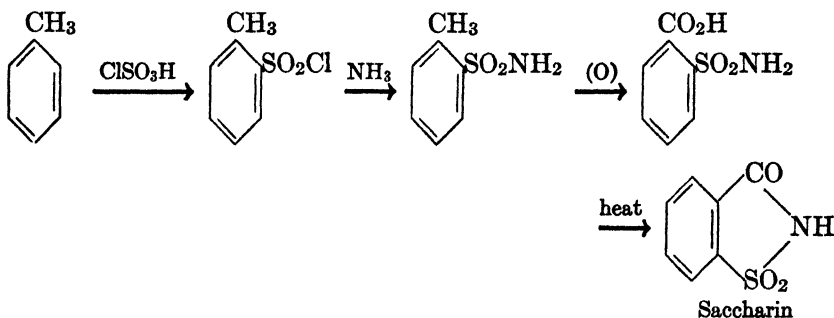
Direct esterification of sulfonic acids does not take place; esters are usually made by treating the acid chloride with alcohols in pyridine.

Ammonia and primary and secondary amines react with the chlorides to give amides. Those having a hydrogen atom on the nitrogen atom are soluble in alkali. This is very interesting in view of the fact that these amides cannot enolize without violating the octet rule.

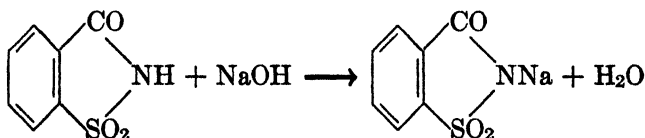
Sulfonamide derivatives have found a variety of uses. Chloramine-T, for example, has antiseptic properties.



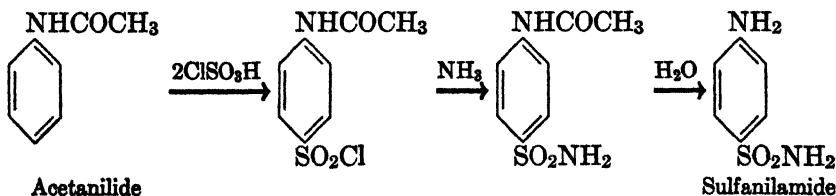
The artificial sweetening agent, saccharin, is closely related to the sulfonamides. It is several hundred times as sweet as sugar and is used by diabetics as a substitute for sugar. It is made from toluene by an interesting sequence of reactions.



Saccharin is a cyclic imide and, like phthalimide, it is a weak acid. It is used in the form of its sodium salt, which is soluble in water.

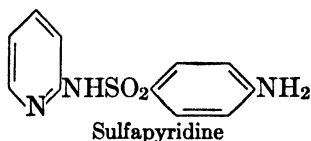


**The Sulfa Drugs.** Certain sulfonamides have been found to be remarkably effective in the treatment of disease. Sulfanilamide has a high bactericidal activity and is particularly valuable in the treatment of streptococcal infections. It is made from acetanilide by the following transformations:

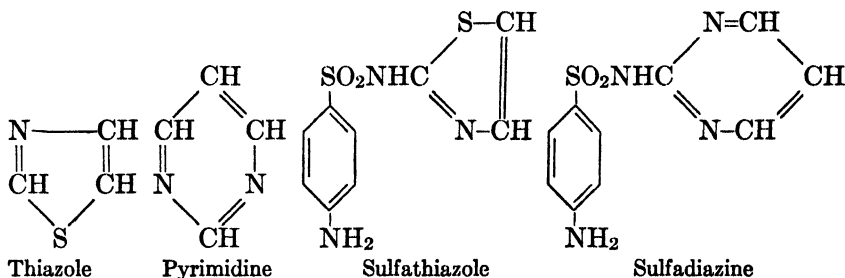


Very closely related to sulfanilamide is sulfapyridine, which has proved amazingly effective in combating pneumonia. It is a derivative

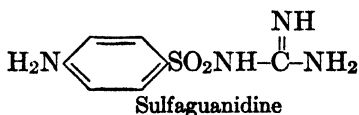
of  $\alpha$ -aminopyridine (p. 456) and is made in much the same way as sulfanilamide.



Sulfathiazole and sulfadiazine promise to be useful drugs particularly for staphylococcal and pneumococcal infections. They differ from sulfapyridine in having thiazole and pyrimidine rings, respectively, instead of the pyridine ring. Thiazole and pyrimidine are among the many less common heterocyclic compounds containing more than one heteroatom. These rings are present in vitamin B<sub>1</sub> or thiamin.



Sulfaguanidine, because it is not absorbed from the alimentary tract, shows promise of being valuable in the treatment of bacillary dysentery and in pre-operative disinfection of the intestinal tract.



### Derivatives of Sulfur Analogs of Carbonic Acid

Only a few of these substances can be mentioned. *Carbon disulfide*, CS<sub>2</sub>, is manufactured by passing sulfur vapors over red-hot coke. It is a volatile, inflammable liquid which finds use as a solvent. It is generally employed in this way in the Friedel-Crafts reaction.

*Carbon oxysulfide*, COS, is made by adding carbon monoxide to sulfur at low temperatures. It is a gas.

The most important derivatives of carbon disulfide are the *xanthates*. They are formed when alkali alcoholates react with carbon disulfide.



These salts are water-soluble, and this fact is used to advantage in the manufacture of rayon from cellulose. The latter is converted to the xanthate and later regained by decomposing the xanthate solution.

*Thiocyanates* are made by adding sulfur to cyanides.



Ferric thiocyanate,  $\text{Fe}(\text{SCN})_3$ , has a deep red color and is used to detect iron. Mercury thiocyanate burns to give Pharaoh's serpents. Alkyl thiocyanates can be made by the action of alkyl iodides or sulfates on potassium thiocyanate.



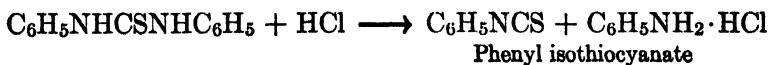
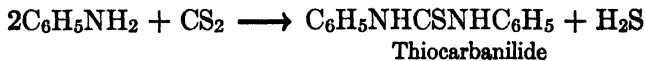
Alkyl thiocyanates and certain of their derivatives are used as contact insecticides. They rearrange to alkyl isothiocyanates when heated. Generally this requires long treatment but in the case of allyl thiocyanate takes place readily. One distillation is sufficient to effect the conversion.



*Isothiocyanates* or *mustard oils* take their name from allyl isothiocyanate which occurs as a glucoside in mustard. The general methods for making them involve the use of primary amines. These are treated with carbon disulfide and lead nitrate.

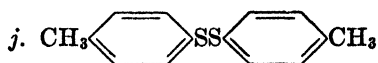
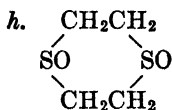
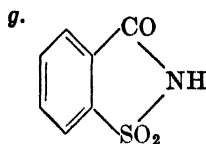
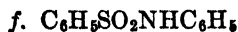
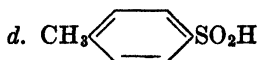
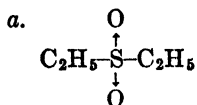


If aniline is heated with carbon disulfide *thiocarbanilide* is formed. It yields phenyl isothiocyanate when boiled with strong hydrochloric acid.



## PROBLEM

Suggest possible methods for obtaining the following compounds:



## SUGGESTED READINGS

GIBSON, "Significant Studies in the Organic Chemistry of Sulfur," *Chem. Rev.*, **14**, 431 (1934).

NORTHEY, "Structure and Chemotherapeutic Activities of Sulfanilamide," *Chem. Rev.*, **27**, 85 (1940).

## CHAPTER XXXI

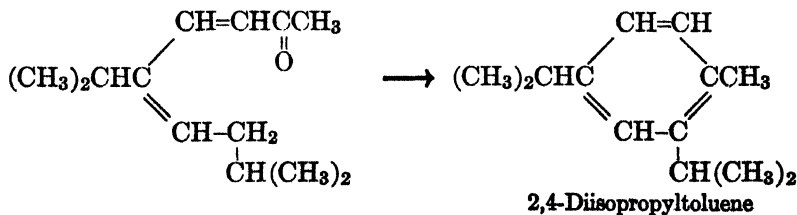
### AROMATIC COMPOUNDS

Aromatic character or aromaticity has always been associated with certain types of reactions more or less peculiar to benzene and its derivatives. Among these are halogenation, nitration, mercuration, sulfonation, the Friedel-Crafts reaction, and coupling with diazonium salts. However, all these reactions are encountered in the aliphatic series and provide no very satisfactory basis for distinguishing between the two classes.

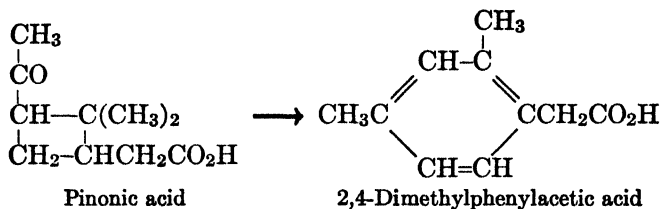
The most important characteristics of aromatic compounds—those which set them off from the aliphatic group—are to be found in their low degree of unsaturation, their tendency to form, and their remarkable ability to retain their peculiar character.

Although benzene can be hydrogenated and will react additively with halogens—is therefore clearly an unsaturated hydrocarbon—it does not decolorize alkaline permanganate solutions. Moreover it tends to undergo substitution rather than addition reactions. Aromatic compounds differ chiefly from unsaturated aliphatic compounds in having only a slight tendency to form compounds of the dihydrobenzene type. In some aromatic compounds such as pyridine and nitrobenzene only substitution occurs and that with difficulty. These compounds are more aromatic than benzene. On the other hand naphthalene gives derivatives of the dihydrobenzenoid type more readily than does benzene and is, accordingly, regarded as less aromatic than benzene.

The formation of aromatic nuclei from aliphatic or alicyclic compounds is a remarkable phenomenon. Sometimes it occurs in ways which do not seem peculiar but more often it involves transformations bespeaking a conspicuous tendency for this type of ring to develop. By way of illustration and contrast may be cited the formation of 2,4-diisopropyltoluene and of 2,4-dimethylphenylacetic acid.

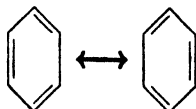




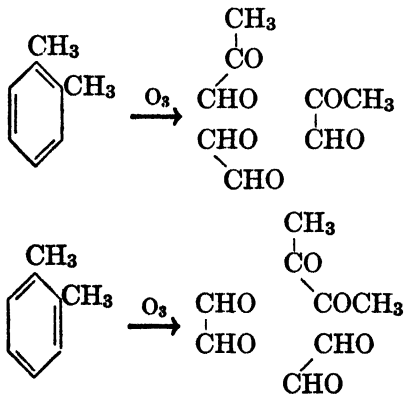


### The Structure of Benzene

It will be noted that on the basis of the vinylogy principle the first example would be expected to form methyl-diisopropylcyclohexatriene. In general, reactions which might be expected to give cyclohexatriene yield benzene or one of its derivatives. It is now generally believed that benzene is, in fact, cyclohexatriene—that it has the structure suggested by Kekulé. Recent studies in wave mechanics indicate that the peculiarly diminished unsaturation of the ring is due to resonance. Thus benzene is pictured as a symmetrical ring which is a resonance hybrid of the two forms resulting from a shift of the bonds.



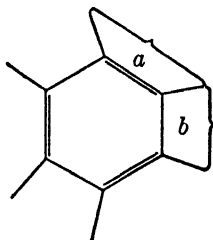
The Kekulé structure is supported also by results obtained by ozonization of *o*-xylene. The two possible modifications are both present, for the products of ozonization include glyoxal, methylglyoxal, and biacetyl.



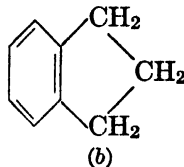
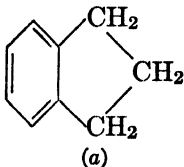
### The Mills-Nixon Effect

The demonstration that *o*-xylene really exists in the two forms possible according to Kekulé's formula might appear to be conclusive

evidence against this formula. On the other hand, there is now evidence that the bond structure of the benzene ring can be stabilized—an observation which only the Kekulé formula can explain. The new work is due to Mills and Nixon, who calculated that the six bonds holding the hydrogen atoms of benzene do not extend from the ring in an entirely symmetrical manner, but that those separated by a double bond form a somewhat larger angle with one another than those separated by a single bond, that is, the distance *a* in the figure is greater than distance *b*.

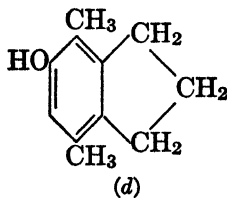
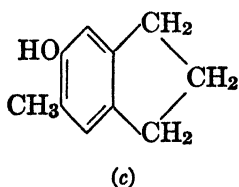


This hypothesis suggests that if a five-membered ring is fused on the benzene ring, as in hydrindene, the strain involved will be less if there is a single rather than a double bond common to the two rings.



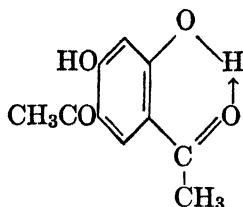
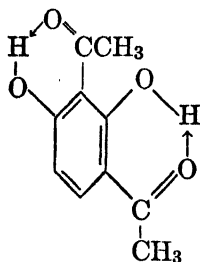
Thus form *a* should be more stable than *b*, and the bonds would tend to become fixed.

Experiments show that such fixation probably occurs. A few facts may be cited as illustrations. Compound *c* couples with diazonium salts much less readily than does *d*.



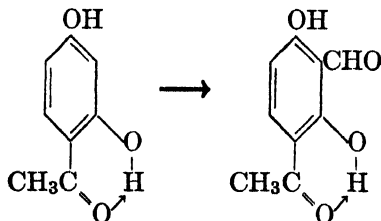
The wide difference in the physical properties of 2,4- and 4,6-diacetyl-resorcinols has been ascribed to chelation. The former melts at 91° and is volatile with steam, whereas the latter melts at 182° and is not volatilized by steam. It will be seen that if we use the Kekulé structure

only one chelate ring is possible in the 4,6-isomer whereas two can be present in the 2,4-derivative.



This, of course, involves the assumption that chelation takes place only when there is a double bond between the hydroxyl group and the acetyl group which are involved.

The introduction of the aldehyde group into resacetophenone by the Gattermann reaction gives the 3- rather than the 5-derivative. This has been explained by assuming fixation of the bonds by chelation.



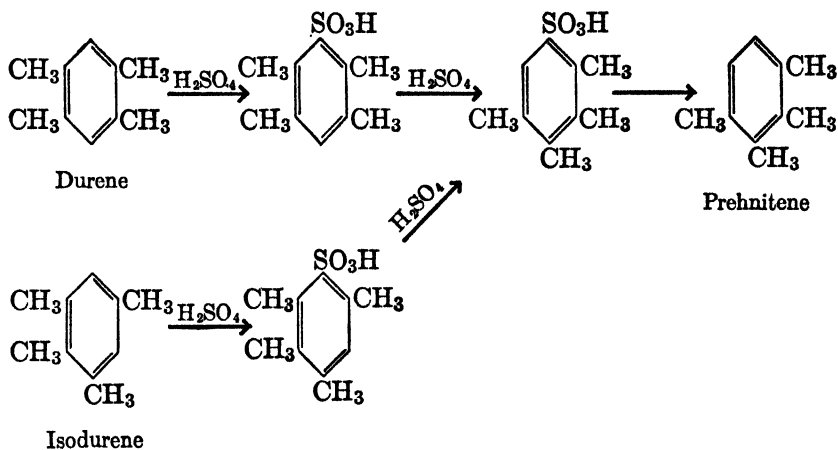
### Reactions of Aromatic Compounds

The reactions involving functional groups attached to an aromatic ring are generally similar to those observed with the aliphatic analogs. However, many exceptions to this rule have been recorded. Some of these have already been discussed; others which are of considerable interest will be mentioned briefly.

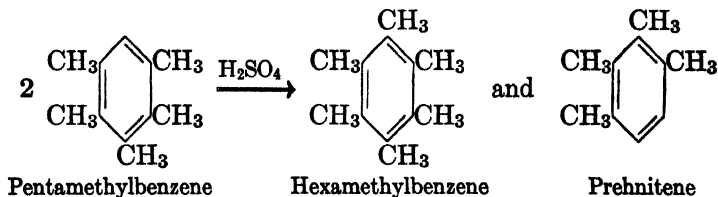
**Side Chains.** Side chains owe their reactivity to the adjoining ring and are much more easily attacked than are paraffins. Not only can they be halogenated (p. 233), but with strong oxidizing agents they are converted to carboxyl groups (pp. 40, 86). As has been seen the reactivity is greatly enhanced by nitro groups in the *ortho* or *para* positions.

A remarkable peculiarity of *o*-dialkylbenzenes is that, in contrast to the *meta* and *para* isomers, they are completely oxidized by chromic acid. With this reagent *o*-xylene is destroyed whereas *m*-xylene gives isophthalic acid. No explanation has been advanced for this difference

During the process of sulfonation, highly alkylated benzenes readily undergo isomerization due to the migration of groups. This is called the Jacobsen rearrangement. In the presence of cold concentrated sulfuric acid the groups may move from one position to another or from one ring to another. For example, prehnitene is obtained from durene or isodurene by the following sequence of changes

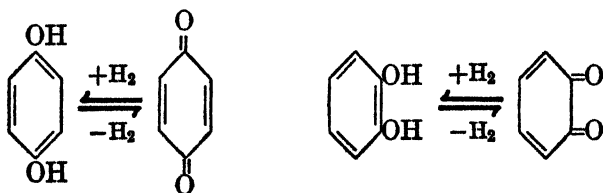


Pentamethylbenzene, on the other hand, yields a mixture of hexamethylbenzene and prehnitene.

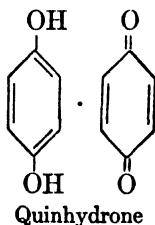


It has been shown that in these migrations the sulfonic acids and not the original hydrocarbons undergo the rearrangement.

**Polyatomic Phenols.** Aromatic rings which carry more than one hydroxyl group exhibit many peculiarities. For example, *o*- and *p*-di-hydroxy compounds are readily oxidized to the corresponding quinones

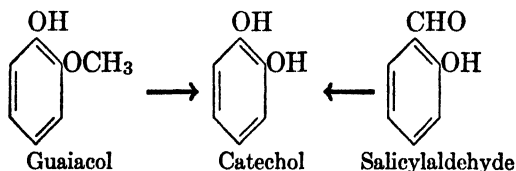


With the quinones they form highly colored addition compounds known as quinhydrones.



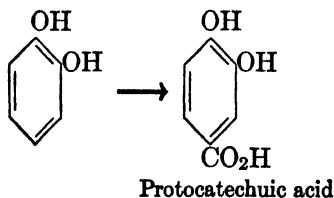
The attachment of the two molecules in the quinhydrone is not understood but appears not to involve primary valence forces. *Meta* dihydroxy compounds cannot give quinones.

**Catechol.** Catechol may be made by demethylation of guaiacol, which occurs in beechwood tar.



A more unusual synthesis is the conversion of salicylaldehyde to catechol by the action of alkaline hydrogen peroxide.

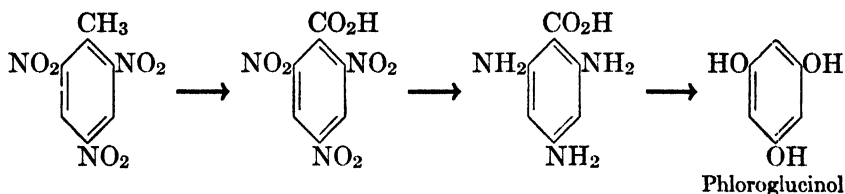
Catechol is remarkable for the ease with which it is carboxylated. It is converted to protocatechuic acid merely by heating with aqueous ammonium carbonate at  $140^{\circ}$ .



**Resorcinol.** Resorcinol results from the alkali fusion of *m*- or *p*-benzenedisulfonic acid or of *o*-, *m*-, or *p*-bromobenzenesulfonic acid. Possibly in the latter examples the sulfonic acid group migrates to the *meta* position before replacement occurs.

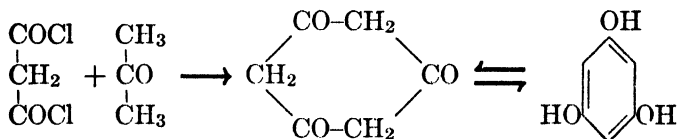
**Phloroglucinol.** Phloroglucinol is obtained in several ways, of which three will be listed.

1. Hydrolysis of 1,3,5-triaminobenzene or 2,4,6-triaminobenzoic acid. The starting point in this synthesis is TNT and the steps are as follows:

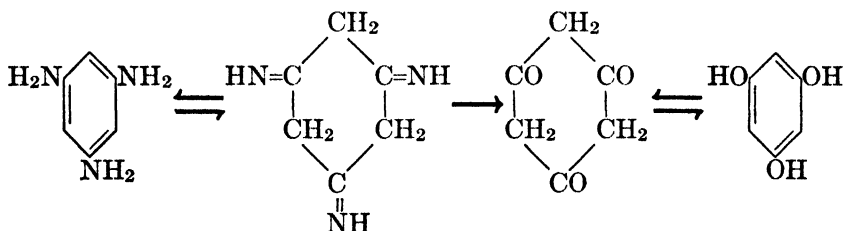


2. Alkali fusion of resorcinol in the presence of air. This is a characteristic of many phenolic substances but it is not clear why the entering hydroxyl group takes up position 5 rather than some other.

3. Condensation of malonyl chloride with acetone.

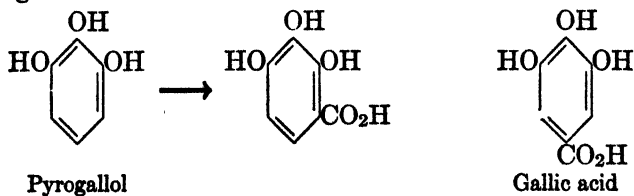


This is especially interesting because it would seem to involve the intermediate formation of the keto form of the phenol. As a matter of fact phloroglucinol yields a trioxime and must exist to some extent in the keto form. This suggests an explanation of the facile hydrolysis of 1,3,5-triaminobenzene. By analogy with oxygen derivatives the triamine would be expected to be in tautomeric equilibrium with the triketimine, a substance which would be hydrolyzed readily.



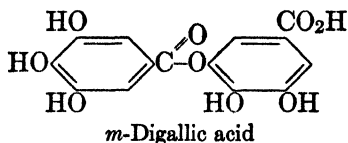
Phloroglucinol is thus very near the borderline which divides aromatic from alicyclic compounds, being under suitable conditions a mixture of tautomers one of which is aromatic and the other alicyclic.

The vicinal (1,2,3-) trihydroxybenzene, known as pyrogallol, is important as a developing agent and as a dye intermediate. It resembles resorcinol in the ease with which it can be carboxylated to give the corresponding acid.



Gallic acid is an isomer of this acid and is obtained from tannic acid, a constituent of gallnuts. The tannic acid of commerce is gallotannin. It is used as a mordant in dyeing cotton cloth (p. 465), in the manufacture of inks, as an astringent, and in the treatment of burns.

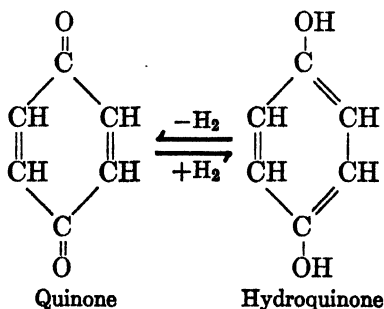
*m*-Digallic acid is a depside and closely related to certain types of tannins.



Depside are esters of aromatic hydroxy acids with hydroxy acids. By esterification of glucose with gallic acid and *m*-digallic acid compounds are formed which resemble natural tannins.

Hydrolysis of natural tannins of this type yields gallic acid. Like pyrogallolcarboxylic acid, gallic acid loses carbon dioxide when heated and yields pyrogallol.

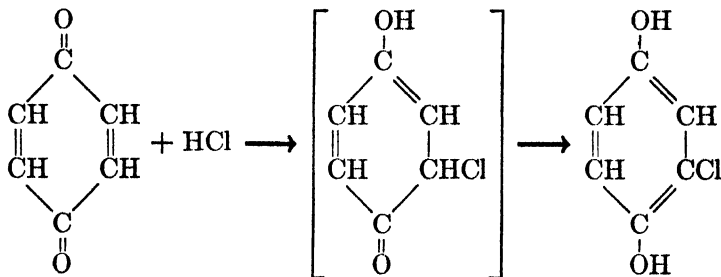
**Quinones.** Quinones are readily formed from certain aromatic compounds and yield dihydroxybenzenes on reduction. The oxidation of aniline with potassium dichromate is one of the common methods for making quinone. The change from quinone to hydroquinone is rapid and reversible, and is one of the few such reactions of organic compounds.



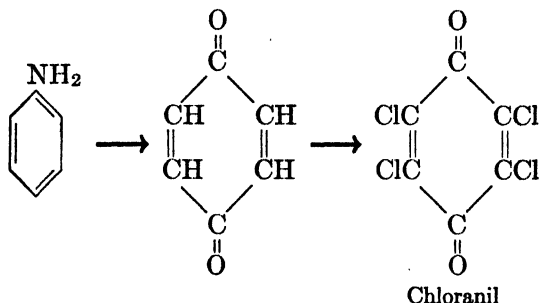
A potential is developed on a platinum wire dipped into a quinone-hydroquinone mixture in the presence of an electrolyte such as dilute acid. This system can function as a half cell.

In spite of this close genetic relationship between a quinone and a hydroquinone it must be recognized that whereas the latter is typically aromatic the former is alicyclic. It is an unsaturated diketone. Quinone undergoes reactions which are characteristic of  $\alpha,\beta$ -unsaturated ketones. For example, hydrogen chloride adds to it in the 1,4 manner

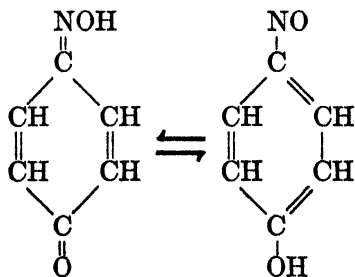
The product is the chlorohydroquinone formed by subsequent enolization.



In the presence of an oxidizing agent the chlorohydroquinone is changed to the corresponding quinone. This process is repeated until the tetrachloroquinone is formed. This explains the formation of chloranil by the oxidation of aniline in the presence of hydrochloric acid.



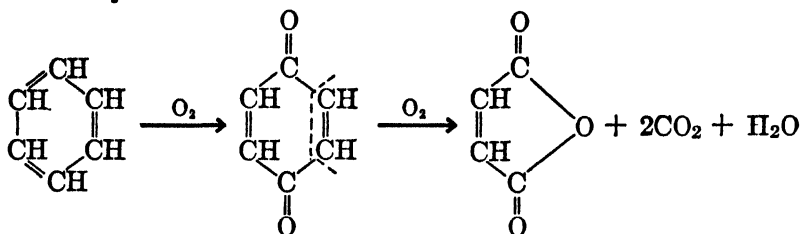
The ketonic nature of quinones is demonstrated by the formation of dioximes and other typical derivatives of diketones. The monoxime of quinone is identical with the product obtained by the action of nitrous acid on phenol. Nitrosophenol and quinone oxime are evidently tautomers; which form represents the product is not yet certain.



Although quinone is generally made by the oxidation of hydroquinone or aniline it can be obtained from benzene directly. It has been

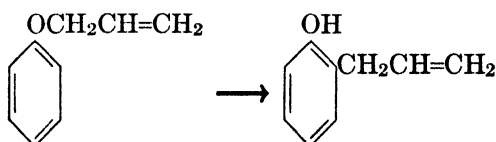


postulated as an intermediate in the catalytic oxidation of benzene to maleic anhydride.

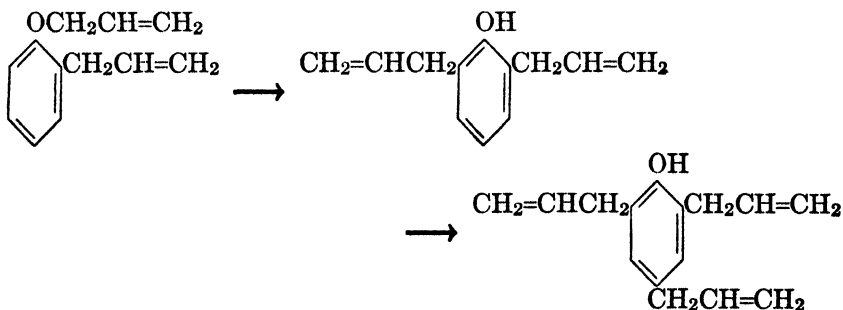


It can be demonstrated that, under the conditions used, quinone will yield the observed products.

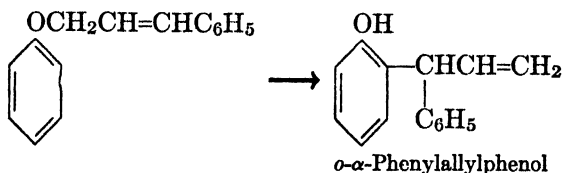
**Rearrangement of Allyl Phenyl Ethers.** Allyl phenyl ethers rearrange under the influence of heat to give the corresponding *o*-allylphenols. The rearrangement was discovered by Claisen and generally bears his name. *o*-Allylphenol is obtained in yields of 80 per cent by heating allyl phenyl ether at 190–220° for six hours.



If the resulting phenol is allylated the rearrangement can be repeated until the *ortho* and *para* positions are filled.

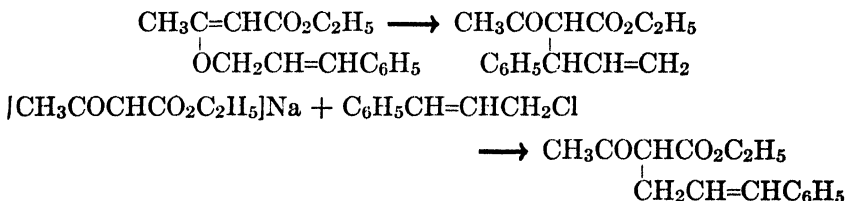


In general the allyl group goes to an *ortho* position but if both these are filled it migrates to the *para* position. It has been established also that the carbon atom which is attached to the oxygen atom in the ether is not the one which becomes attached to the ring; the  $\gamma$ -carbon atom of the allyl group is joined to the aromatic nucleus in the rearrangement product. This is illustrated by phenyl cinnamyl ether which yields not cinnamylphenol but *o*- $\alpha$ -phenylallylphenol.

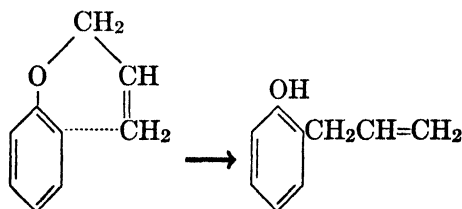


The rearrangement of allyl phenyl ethers is general and is remarkable for the simplicity of the procedure and the excellence of the yields. This type of reaction has been observed with other phenyl ethers and also with vinyl allyl ethers.

An interesting example of the same sort is the rearrangement of the cinnamyl ether of ethyl acetoacetate. The product is not identical with that which is formed by treatment of the sodium derivative of ethyl acetoacetate with cinnamyl chloride. This shows that the enol ether cannot be intermediate in the formation of ethyl cinnamylacetoacetate.

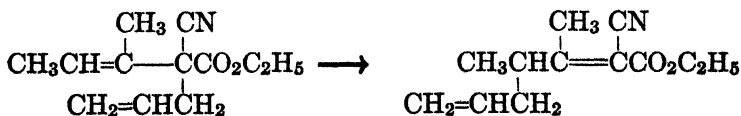


The inversion of the allyl group during rearrangement to the *ortho* (or *gamma*) position suggests that some sort of ring closure may be involved.



Support for this idea is seen in the fact that when the group migrates to the *para* position, where ring closure is impossible, inversion rarely takes place.

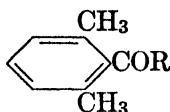
A reaction that bears a remarkable resemblance to the Claisen rearrangement has been observed in the aliphatic series. It involves the isomerization of allyl alkylene derivatives of certain active methylene compounds. The following is an illustration.



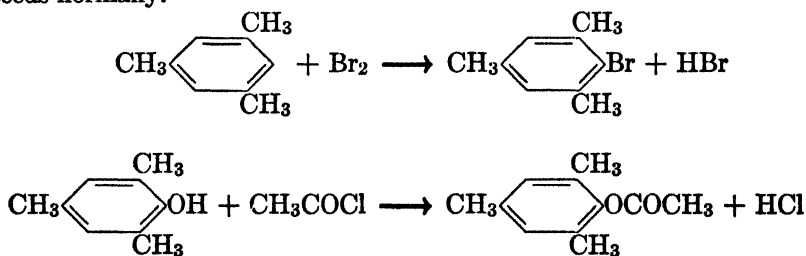
The rearrangement is peculiar in that the migrating radical goes from one carbon atom to another. However, this is in harmony with the fact that atoms attached to the  $\alpha$ -carbon atom in malonic, acetoacetic, and cyanoacetic esters tend to be very mobile.

**The Ortho Effect.** It is a familiar observation that the behavior of substituents on the benzene ring may be more or less profoundly influenced by the atoms or groups of atoms which are in the adjacent positions. These variations from the normal, taken collectively, are referred to as the *ortho effect*. It is one of many effects ascribed to steric hindrance. The only data which are in any sense quantitative are the rates of racemization of certain optically active biphenyls. These rates seem to be proportional to the space-filling properties of the *ortho* groups involved. This evidence supports the theory that nonrotation about the single bond is a purely steric effect.

Other observations are not only less exact but also more difficult to explain on the basis of space considerations. One important generalization can be made, however. Reactions which are of the additive type appear to be slowed down or inhibited whereas substitution reactions usually are unaffected. For example, ketones of the type



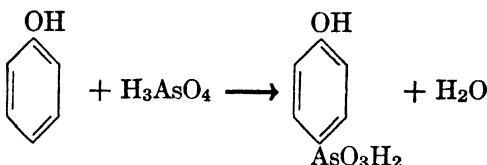
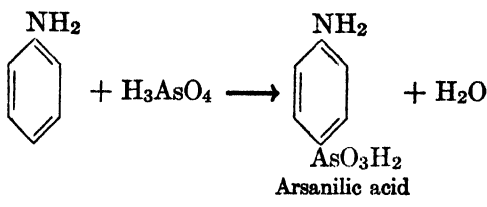
fail to give the usual reactions of the carbonyl group. On the other hand the bromination of mesitylene or the acetylation of mesitol proceeds normally.



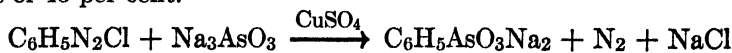
### Substitution Reactions

In addition to halogenation, nitration, sulfonation, and other substitution reactions that have already been discussed, there are two others that should be mentioned here. These are arsonation and mercuriation.

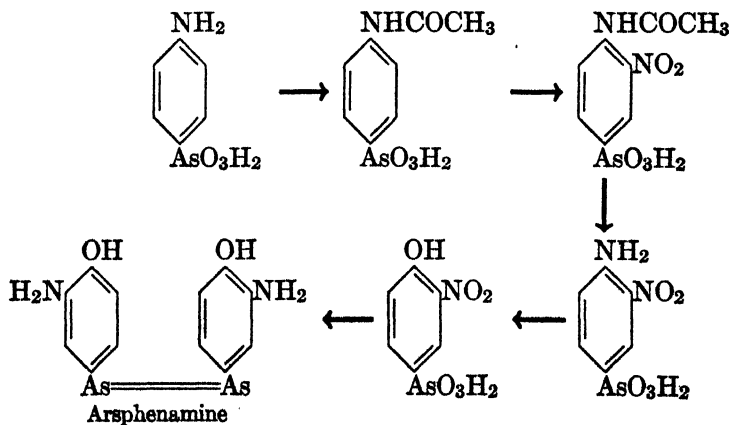
**Arsonation.** Aromatic amines and phenols react with arsenic acid to yield the corresponding amino and hydroxy arsonic acids.



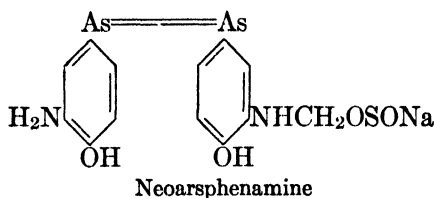
In each instance the principal product is the *para* isomer. Small amounts of the *ortho* isomers are also produced. A more general method of making arsonic acids is furnished by the Bart reaction. This reaction takes place when a diazonium salt is decomposed in the presence of sodium arsenite or arsenic trichloride and a copper salt. Phenylarsonic acid can be made from benzenediazonium chloride and sodium arsenite in yields of 45 per cent.



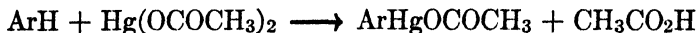
The value of arsonation in synthetic work may be illustrated by reference to arspenamine and neoarsphenamine. The discovery of arspenamine or salvarsan was one of the early triumphs in the history of chemotherapy. This compound is also called "606" because it was the 606th arsenical tried by its discoverer, Ehrlich. It has proved to be extremely useful in the treatment of syphilis. It is made from arsanilic acid by the following method:



From a practical viewpoint, arsphenamine has several disadvantages. For example, it is so easily oxidized that it deteriorates in contact with the air. Many attempts have been made to find a derivative in which these undesirable properties are minimized. One of these is neoarsphenamine, which is made by treating arsphenamine with a solution of the addition compound formed by formaldehyde and sodium hydrosulfite. It appears to have the following structure:

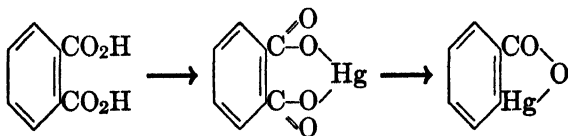


**Mercuration.** One of the most interesting substitution reactions of aromatic compounds is the direct introduction of a mercuri acid group such as acetoxymercuri. This can be brought about by treatment with mercuric acetate, or, what amounts to the same thing, mercuric oxide in acetic acid.



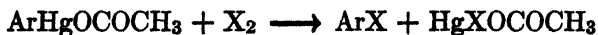
Hydrocarbons are mercurated by treatment at 90–160° for one or more hours. Amines and phenols react very much more readily. Nitro compounds and aryl halides undergo mercuration with difficulty.

Acids are usually mercurated by refluxing the sodium salt with aqueous mercuric acetate solution until no ionic mercury remains in solution. When *o*-phthalic acid is used, one of the carboxyl groups is replaced.



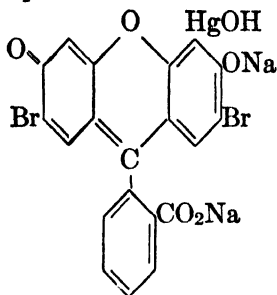
Mercuration, like nitration and sulfonation, may give mono-, di-, or polysubstituted derivatives. Monosubstituted aromatic compounds such as phenol and aniline yield *ortho* and *para* derivatives as would be expected. Substitution is abnormal, however, with compounds that have *meta*-directing groups. For example, nitrobenzene yields 52 per cent of the *ortho*, 38 per cent of the *meta*, and 9 per cent of the *para* derivative.

The position taken by the acetoxymercuri group can be determined by treatment with halogens, which replace the group by halogen.

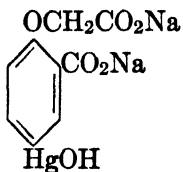


Bromine, iodine, and iodine monochloride are used most often for this purpose.

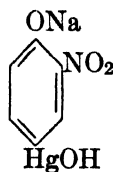
The interest in mercury compounds has centered around their use in medicine. Among the many compounds which have been developed may be mentioned the disinfectants, mercurochrome, mercurosals, and mercurophen.



Mercurochrome



Mercurosals



Mercurophen

### PROBLEMS

1. What reasons can you give for classifying quinones as aliphatic compounds? as aromatic compounds?
2. What are *vicinal* trisubstituted benzene derivatives?
3. Indicate a method of synthesis for prehnitene.

### SUGGESTED READINGS

FIESER, "Theory of the Structure and Reactions of Aromatic Compounds," Gilman's *Organic Chemistry*, Chapter 2, John Wiley and Sons, New York, 1938.

HURD, *The Pyrolysis of Carbon Compounds*, Chemical Catalog Company, New York, 1929, p. 214 *et seq.*

*Annual Reports of the Chemical Society*, **1922**, 96.

TARBELL, "The Claisen Rearrangement," *Chem. Rev.*, **27**, 495 (1940).

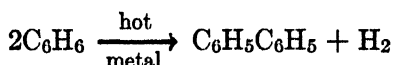
PRICE, "Substitution and Orientation in the Benzene Ring," *Chem. Rev.*, **29**, 37 (1941)

## CHAPTER XXXII

### POLYNUCLEAR AROMATIC HYDROCARBONS

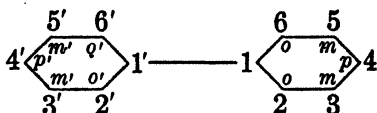
Similarities rather than differences have been stressed in discussing properties common to aliphatic as well as aromatic compounds. Recent studies have done much to break down the line of demarcation which formerly separated these two classes of substances. It is becoming increasingly apparent that their differences are of degree rather than of type. Yet the benzenoid structure permits the formation of condensed nuclei and offers certain other peculiarities which as yet have no close parallel in the aliphatic series. These appear in sharp relief in the polynuclear aromatic hydrocarbons and their derivatives. These are among the most useful and most interesting types of organic compounds, and include naphthalene, biphenyl, triphenylmethane, anthracene, phenanthrene, and numerous similar substances.

**Biphenyl.** Biphenyl was made formerly by treating bromobenzene with sodium, but is now prepared on a commercial scale by bringing benzene into contact with a hot metal.



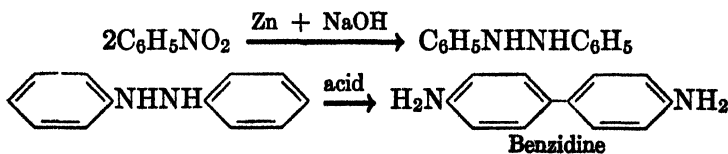
This hydrocarbon is stable at its boiling point (254°) and is useful where a high-boiling liquid is required.

Derivatives of biphenyl are named according to either of the two systems shown in the following figure:



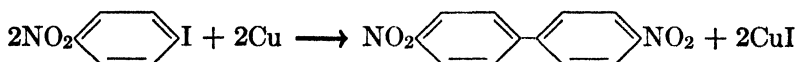
Thus  $\text{NO}_2$   $\text{NO}_2$  is called 4,4'- or *p,p'*-dinitrobiphenyl.

The most useful derivative of biphenyl is benzidine, obtained by the rearrangement of hydrazobenzene, a reduction product of nitrobenzene.



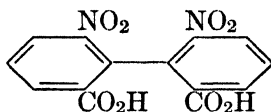
Benzidine is used in the preparation of certain dyes which are direct for cotton. These will be mentioned later.

Many biphenyl derivatives are most conveniently made by means of Ullmann's method, which involves the treatment of halobenzenes with copper powder (p. 251).



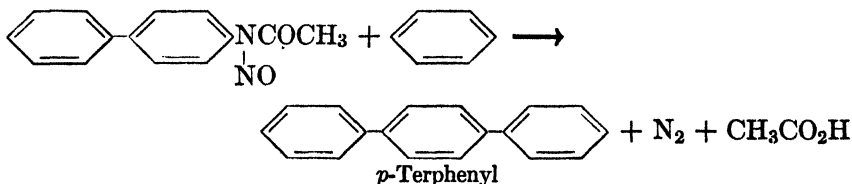
The halogen atom must be active, and for this reason iodo compounds are commonly employed.

Derivatives of biphenyl in which both rings are unsymmetrically substituted and which contain groups in the *ortho* positions that prevent free rotation about the central linkage have been shown to possess optical activity. An example is 6,6'-dinitro-2,2'-dicarboxybiphenyl.

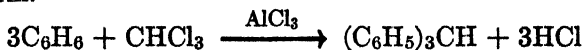


*p*-Bromobiphenyl is made by treating benzene with *p*-bromobenzene-diazonium chloride in the presence of sodium hydroxide.

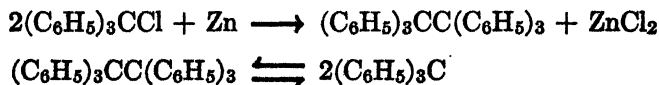
**Terphenyl.** The best method of synthesis for terphenyl and its derivatives depends on a condensation reaction between an aromatic hydrocarbon or ether with an *N*-nitrosoacetylarylamine. Benzene and the nitroso derivative of 4-acetaminobiphenyl give terphenyl.



**Triphenylmethane.** This hydrocarbon is made by condensing benzene with chloroform.

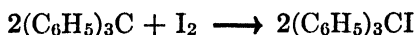
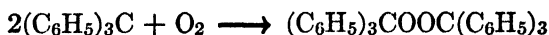


A derivative of great interest is the free radical, triphenylmethyl. When triphenylmethyl chloride in benzene solution is treated with zinc, hexaphenylethane is formed; this extraordinary hydrocarbon dissociates to some extent into triphenylmethyl.

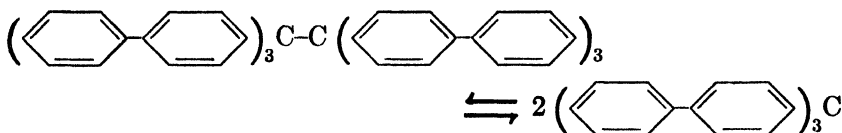




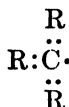
This dissociation is evidenced by color formation which increases with temperature. The free radical is not only colored but also extremely reactive. Two of its reactions are listed below.



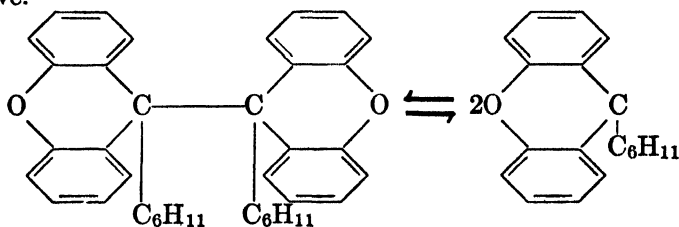
Actually the amount of dissociation of hexaphenylethane is very small. Hexabiphenylethane, however, is almost completely dissociated in the solid form.



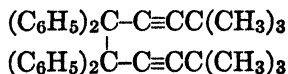
As has been stated previously the free radicals are odd molecules and owe their color and great reactivity to the lone electron.



It has been demonstrated that six aryl groups are not necessary to produce dissociation. Four aryl and two alkyl groups may give the same effect. Substitution of alkyl groups for the two hydrogen atoms in bi-xanthyl brings about dissociation. Cyclohexyl groups are particularly effective.

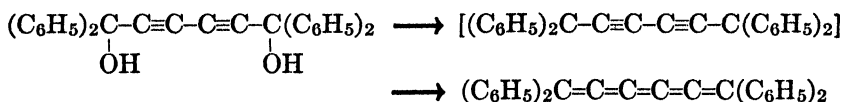


Alkylethyne groups appear to exert a similar influence. The central linkage in *sym.*-tetraphenyldi-(*t*-butylethyne)-ethane, for example, is very weak, being cleaved by alkali metals.



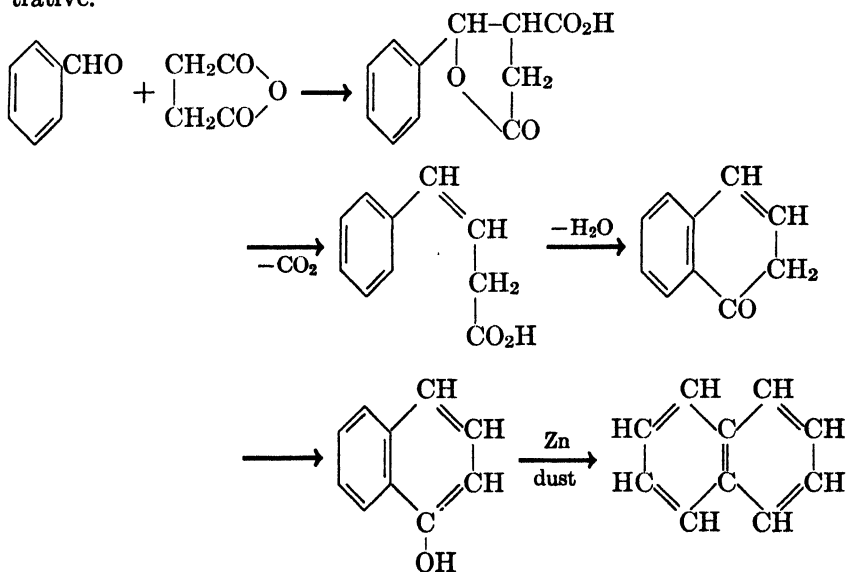
This observation calls to mind Kuhn's remarkable synthesis of cumulenes. The acetylenic glycol derived from diacetylene and benzophe-

none is treated with hydrogen chloride and chromous chloride. Presumably a biradical forms and rearranges to the cumulene.

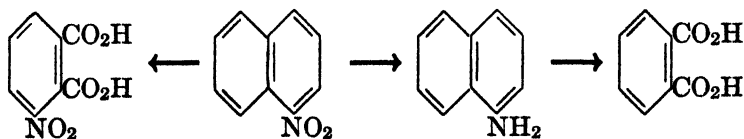


The cumulenes are more highly colored than conjugated polyenes  $[\text{C}_6\text{H}_5(\text{CH}=\text{CH})_n-\text{C}_6\text{H}_5]$ .

**Naphthalene.** The most abundant constituent of coal tar is naphthalene. It contains two rings fused together, i.e., which have two carbon atoms in common. The evidence for this comes both from methods of synthesis and degradation products. The following synthesis is illustrative.

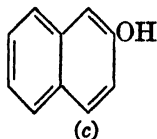
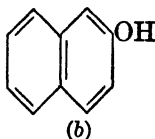
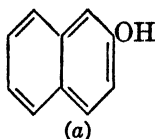


That naphthalene contains two rings is demonstrated by the following degradations:

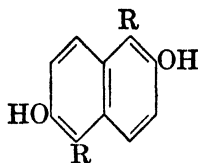
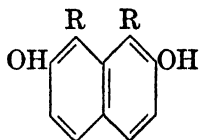


This shows also that both rings are or may become true benzene rings, and leaves the question of the internal structure of naphthalene in much

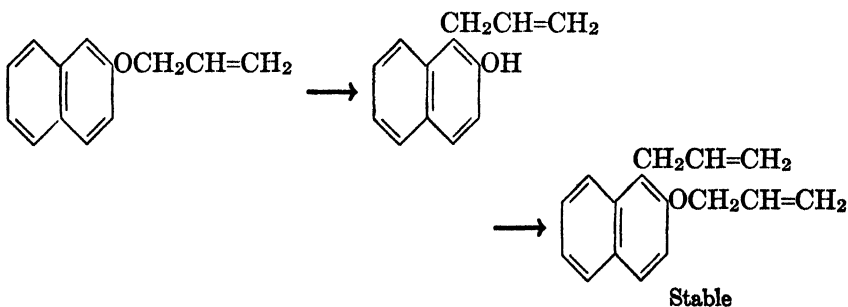
the same state as that of benzene. The following formulas of  $\beta$ -naphthol illustrate the structures commonly used.



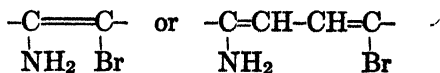
Recent evidence indicates that the Erlenmeyer structure *b* is the correct one and that *a* and *c* probably do not occur to an appreciable extent. For example, the following types of compounds fail entirely to undergo coupling with diazonium salts—a fact which is interpreted to mean that there are only single bonds between carbon atoms 2 and 3 or 6 and 7 (see p. 438 for the method of numbering):



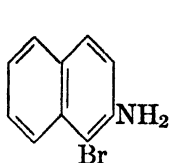
The rearrangement of allyl  $\beta$ -naphthyl ether points to the same conclusion. The allyl group migrates to the  $\alpha$ -position exclusively. Moreover, allyl  $\beta$ -( $\alpha$ -allyl) naphthyl ether does not undergo rearrangement.



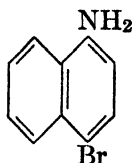
Evidence in favor of the Erlenmeyer formula for naphthalene has been obtained by a study of bromonaphthylamines. In certain of these the bromine atoms are "positive" and can be removed by treatment with stannous chloride and hydrochloric acid. This property appears to be possessed by those compounds containing the grouping



In conformity with this it is found that 1-bromo-2-naphthylamine and 1-bromo-4-naphthylamine are debrominated, whereas 3-bromo-2-naphthylamine is recovered unchanged. 1,3-Dibromo-2-naphthylamine loses only the bromine atom in the 1 position (see p. 438 for the method of numbering).



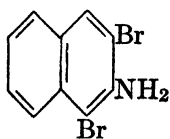
1-Bromo-2-naphthylamine



4-Bromo-1-naphthylamine



3-Bromo-2-naphthylamine



1,3-Dibromo-2-naphthylamine

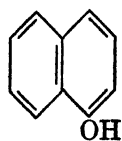
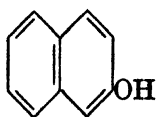
These results are in accord with predictions based on the principle of vinylogy.

A neat proof of the equivalence of positions 1 and 5 is furnished by the demonstration that naphthalene-1,5-disulfinylacetic acid can exist in *meso* and *racemic* forms.

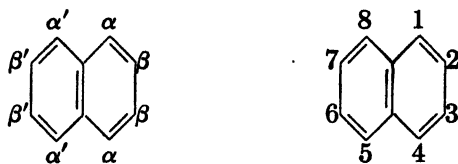


This could be possible only if the nucleus is symmetrical, for the optical activity resides in the sulfur atoms.

Naphthalene yields only two monosubstitution products—a fact which proves that the eight hydrogen atoms must be symmetrically located. These are known as the  $\alpha$  and  $\beta$  forms;  $\alpha$ - and  $\beta$ -naphthol are examples.

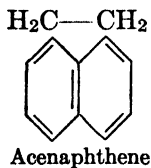
 $\alpha$ -Naphthol $\beta$ -Naphthol

The orientation of naphthalene derivatives is indicated by one of the systems which follow:

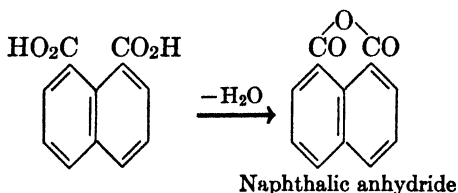


The 4,5 (and 1,8) are often called the *peri* positions.

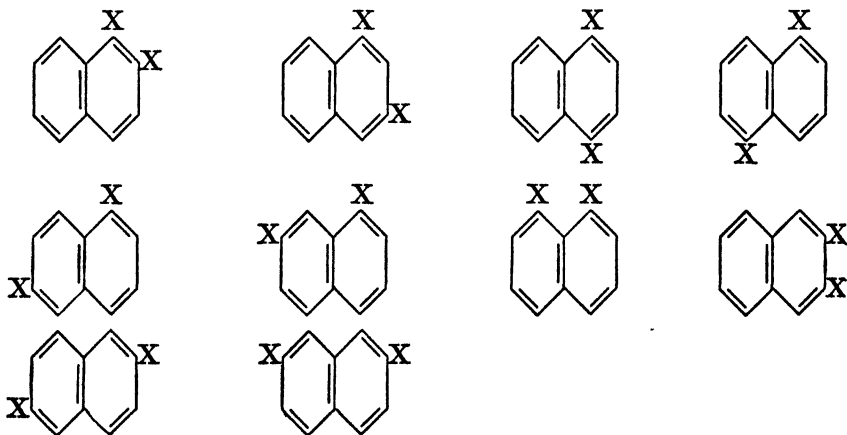
These positions are joined with a two-carbon bridge in acenaphthene, a constituent of coal tar.



Substituents in the *peri* positions may react with each other much as do *ortho* substituents. Naphthalic acid, for example, forms a monomeric anhydride.



Ten disubstitution products are possible if the substituents are alike—fourteen if they are unlike.

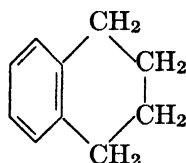


Naphthalene can be halogenated, nitrated, and sulfonated and undergoes the Friedel-Crafts reaction. In all cases  $\alpha$ -substitution products result. The latter two reactions give  $\beta$ -substitution products also.

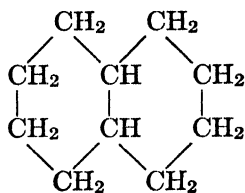
The sulfonation of naphthalene is reversible and gives rise to the  $\alpha$ -iso-

mer at low temperatures (about 80°) and the  $\beta$ - at higher temperatures (about 160°) (p. 42). The  $\alpha$ -compound is transformed into the  $\beta$ - by heating in the presence of sulfuric acid. This is because it is hydrolyzed about fifty times as fast as the  $\beta$ -acid.

Hydrogenation of naphthalene gives the tetra- and decahydro derivatives—generally called, respectively, tetralin and decalin.



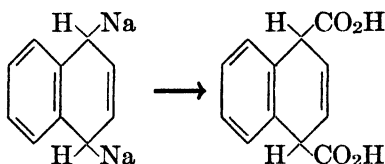
Tetralin



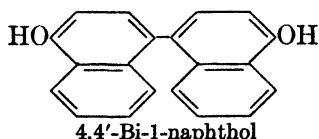
Decalin

These compounds are used as solvents in paints, varnishes, and lacquers. Decalin exists in *cis* and *trans* modifications.

Naphthalene reacts with sodium to give a disodium derivative. Carbonation yields a dicarboxylic acid.

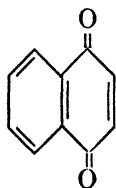
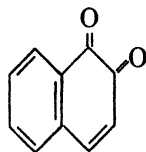
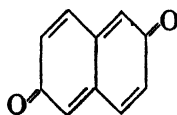


Oxidation of  $\alpha$ -naphthol with ferric chloride gives binaphthol.

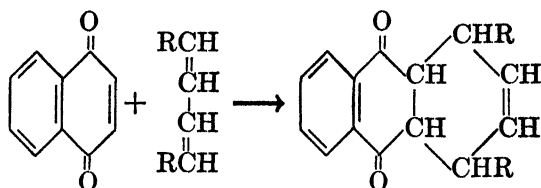


4,4'-Bi-1-naphthol

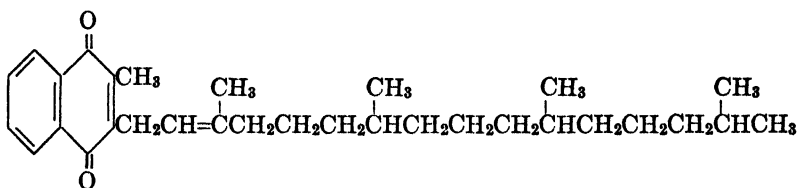
Chromic acid oxidizes naphthols to quinones. Three different naphthoquinones are known.

 $\alpha$ -Naphthoquinone $\beta$ -Naphthoquinone*amphi*-Naphthoquinone

The naphthoquinones are colored and like benzoquinones are easily reduced to colorless dihydroxy derivatives.  $\alpha$ -Naphthoquinone condenses with conjugated dienes to yield derivatives that are usually solid and therefore useful for purposes of identification.



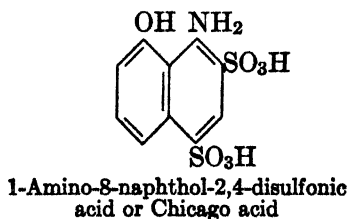
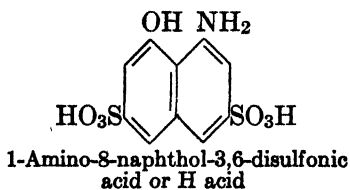
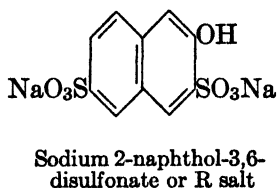
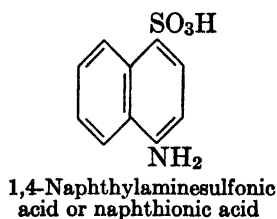
The  $\alpha$ -naphthoquinone nucleus occurs in vitamin K<sub>1</sub>, the antihemorrhagic factor, which has been shown to be 2-methyl-3-phytyl-1,4-naphthoquinone.



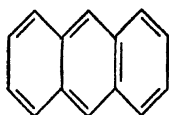
Vitamin K<sub>1</sub>

In vitamin K therapy 2-methyl-1,4-naphthoquinone and certain of its simple derivatives have proved to be as effective as the vitamin itself. It may be that the phytyl group is supplied in the organism.

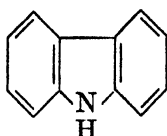
The most important naphthalene derivatives are those used as dye intermediates. Some of these are listed below.



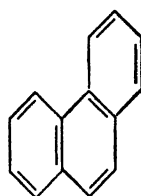
**Anthracene.** Anthracene occurs to the extent of 0.2 to 0.4 per cent in coal tar. When isolated from this source it is always contaminated with carbazole and phenanthrene.



Anthracene



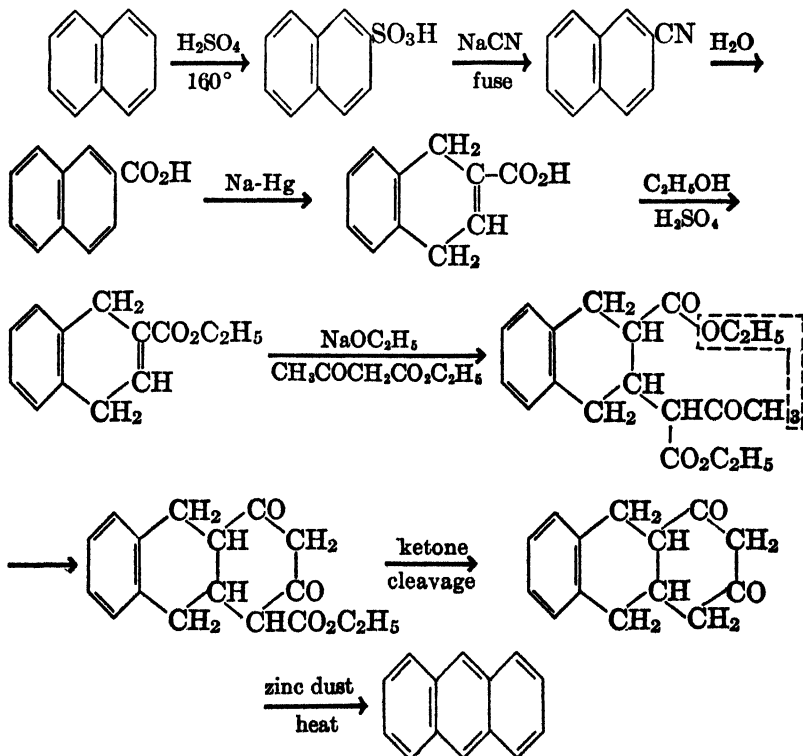
Carbazole



Phenanthrene

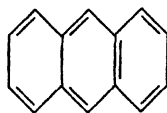
These impurities are very hard to remove and this fact has to some extent diminished the importance of coal tar anthracene as a source of anthracene derivatives. It has been found recently that dimethylacetamide is a good solvent for separating carbazole and anthracene. It dissolves the carbazole, presumably by hydrogen bonding.

Anthracene contains three condensed rings as is shown by the following synthesis:

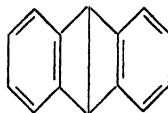




This synthesis does not disclose the arrangement of the bonds. The structures usually written are given here.

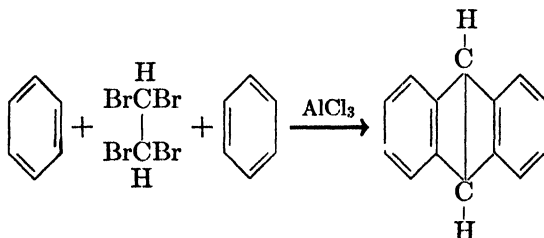


(a)

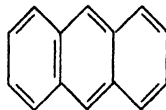
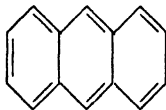
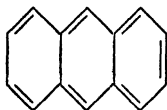


(b)

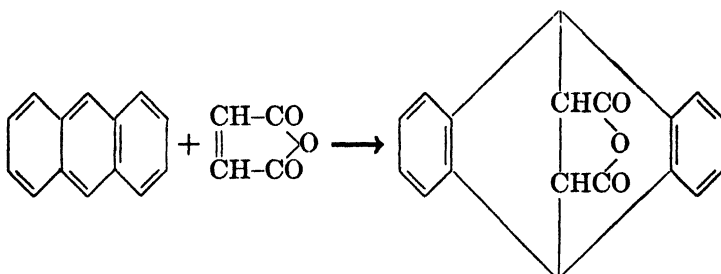
Formula *b* is made to appear plausible by the following synthesis:



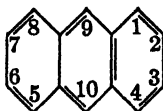
It should be noted, however, that aluminum chloride is very effective in breaking carbon-to-carbon linkages. The evidence shows *a* to be the correct structure. It is one of four possible resonance forms. The others are the following:



Anthracene undergoes the Diels-Alder reaction and, therefore, must have a system of conjugated double bonds in the middle ring.



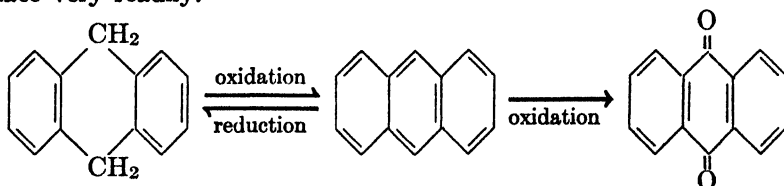
The usual method of naming anthracene derivatives is based on the following number system:



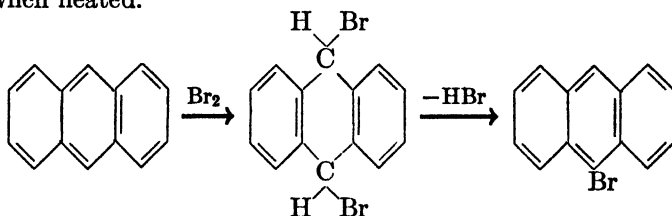
In general, naphthalene is less aromatic than benzene, and anthracene still less so than naphthalene. Reduction and oxidation of

## ANTHRACENE

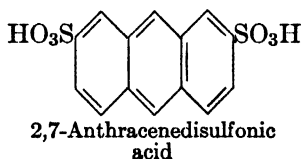
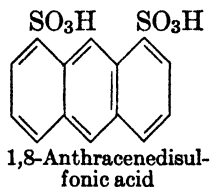
anthracene to the dihydro derivative and the quinone, respectively, ' place very readily.



Bromine attacks the molecule at the 9 and 10 positions, forming an addition compound which is fairly stable but which loses hydrogen bromide when heated.

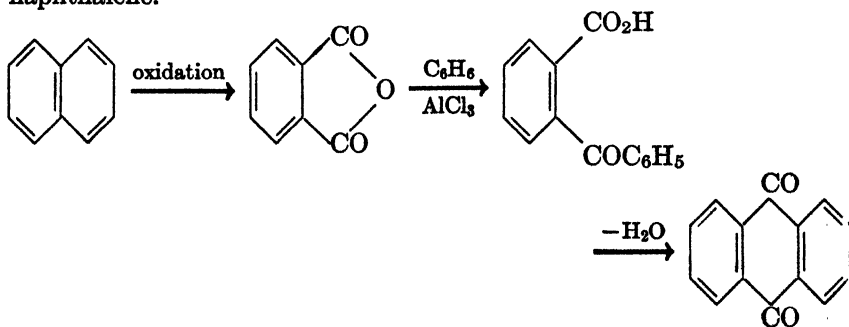


Sulfuric acid sulfonates anthracene, usually yielding a disulfonic acid. At low temperatures this is the 1,8- and at higher temperatures the 2,7-acid.



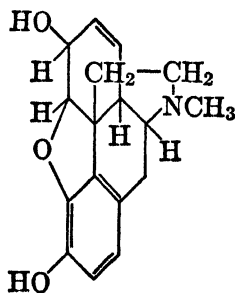
Nitric acid acts not as a nitrating but as an oxidizing agent, giving anthraquinone. This compound is truly aromatic and is the mother substance of the more important anthracene derivatives.

Anthraquinone and many of its derivatives are made by the following type of synthesis which involves not anthracene but benzene and naphthalene.

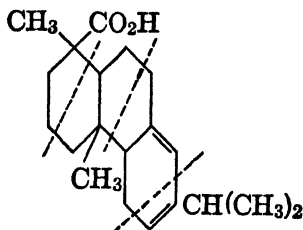


## POLYNUCLEAR AROMATIC HYDROCARBONS

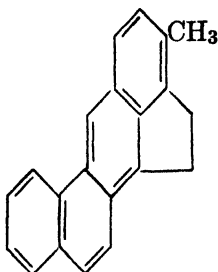
**Phenanthrene.** Phenanthrene is an isomer of anthracene and occurs in coal tar. It has attracted increased attention recently because of the discovery that its skeletal structure occurs in a wide variety of natural substances. The significance of this is made apparent by a glance at the impressive array of types of compounds which have this structural unit in common. Examples are found among morphine alkaloids, resin acids,\* carcinogenic hydrocarbons, sterols, bile acids, sex hormones, heart poisons, and saponins. The following compounds are illustrative.



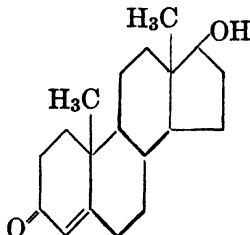
Morphine



Abietic acid

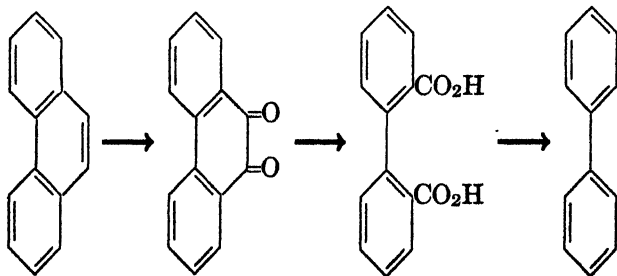


Methylcholanthrene



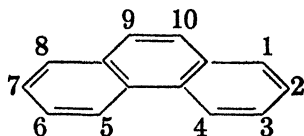
Testosterone

The fact that phenanthrene has three six-membered rings arranged as shown in the formula was proved by the following degradation to biphenyl:



\* It is interesting to observe in passing that the formula of abietic acid obeys the isoprene rule.

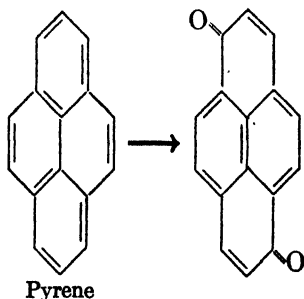
The nomenclature of phenanthrene derivatives is based on the following system:



The foregoing arrangement of the bonds is in accord with the Fries rule, which states that each ring of a polynuclear aromatic compound strives to assume the bond structure which most nearly approaches the condition of an isolated benzene ring. This formula is, in fact, considered to be the most probable one.

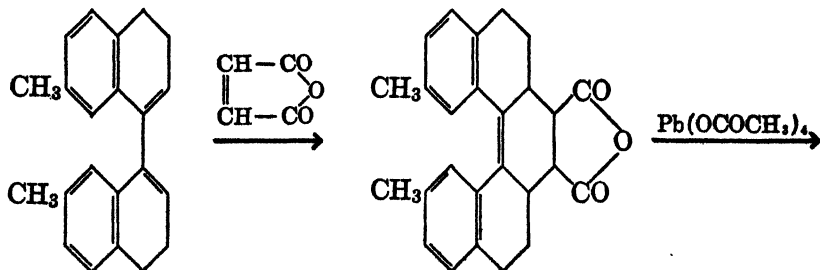
Phenanthrene is more reactive than naphthalene and less reactive than anthracene. It undergoes all the usual reactions of aromatic hydrocarbons such as sulfonation, nitration, and the Friedel-Crafts reaction.

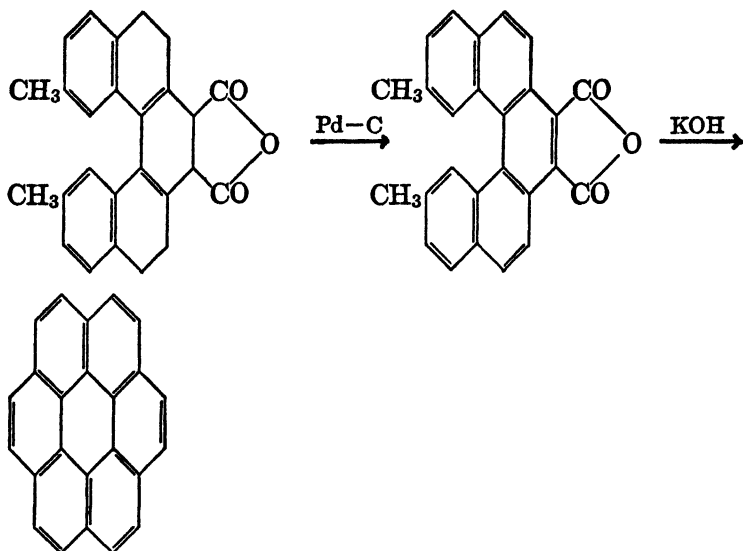
**Other Condensed Polynuclear Aromatic Hydrocarbons.** Many other hydrocarbons of this group are known, and there seems to be no limit to the number of benzenoid rings which may be condensed into a molecule. Striking illustrations are given below.



Pyrene occurs in coal tar. Oxidation converts it to the quinone shown above.

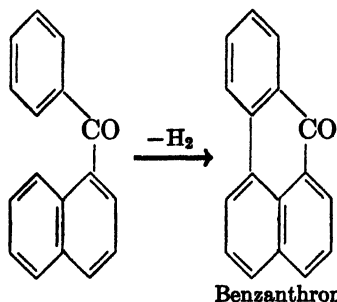
One of the most interesting of the more complex aromatic hydrocarbons is hexabenzobenzene or coronene; it has recently been synthesized by the following transformations:





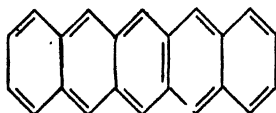
The positions of the double bonds in highly condensed aromatic compounds such as the foregoing are not known with certainty. The most probable arrangement of the bonds is thought to be that which affords the maximum number of truly benzenoid rings.

*The Scholl reaction.* Certain aromatic ketones may undergo intramolecular dehydrogenation under the influence of aluminum chloride. This is the Scholl reaction; it has proved of great value in the synthesis of polynuclear compounds. An example is the conversion of  $\alpha$ -benzoylnaphthalene to benzanthrone.



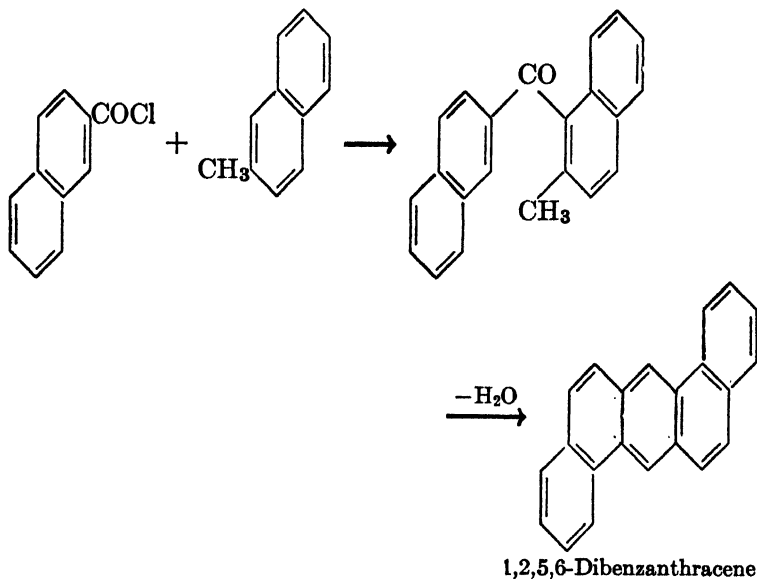
Benzanthrone

2,3,6,7-Dibenzanthracene is blue and exceedingly reactive.



2,3,6,7-Dibenzanthracene

1,2,5,6-Dibenzanthracene has been made from  $\beta$ -naphthoyl chloride by the following sequence of changes:



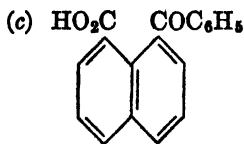
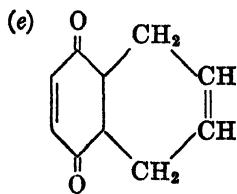
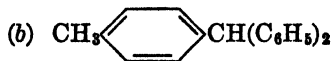
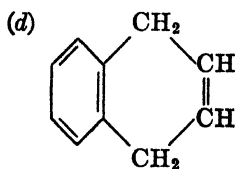
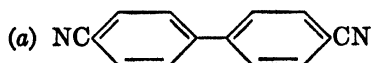
This type of ring closure, known as the Elbs reaction, is general for *o*-alkylbenzophenones and has been used widely in the synthesis of anthracene derivatives. The reaction is induced by heating; it gives low yields.

## PROBLEMS

1. Arrange the following hydrocarbons in the order of decreasing reactivity: toluene, naphthalene, phenanthrene, benzene, anthracene.

2. Suggest an explanation of the fact that the course of the sulfonation of anthracene depends on the temperature.

3. Outline methods of synthesis for the following compounds:



## SUGGESTED READINGS

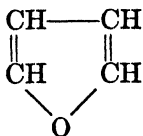
- ADAMS and YUAN, "The Stereochemistry of Diphenyls and Analogous Compounds," *Chem. Rev.*, **12**, 262 (1933).
- FIESER, *The Chemistry of Natural Products Related to Phenanthrene*, Reinhold Publishing Corporation, New York, 1937.
- SANDIN and EVANS, "The Structure of Some Naphthalene, Hydrindene, and Tetralin Derivatives," *J. Am. Chem. Soc.*, **61**, 2916 (1939).

## CHAPTER XXXIII

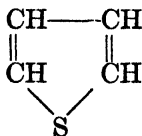
### AROMATIC HETEROCYCLIC COMPOUNDS

Cyclic compounds in which not all the atoms forming the ring are alike are known as heterocyclic compounds. Many of these rings are easily opened and for this reason are classified as aliphatic. Others are very stable and possess many of the properties of the aromatic hydrocarbons. This chapter will deal with this group.

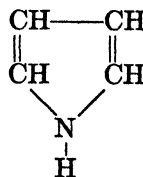
The most important types of heterocyclic compounds are listed below.



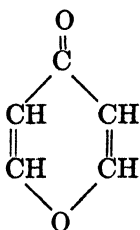
Furan



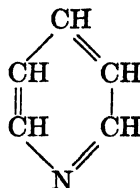
Thiophene



Pyrrole



$\gamma$ -Pyrone



Pyridine

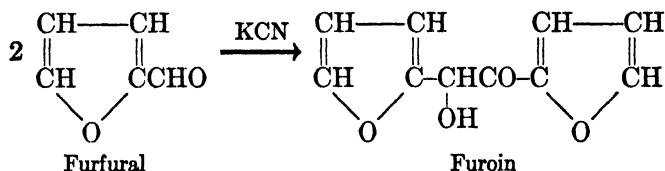
All these substances, except  $\gamma$ -pyrone, undergo reactions typical of aromatic hydrocarbons. They differ in the degree of reactivity which they possess. Some, for example, couple with diazonium salts whereas others fail to do so.

It is easy to understand why pyridine and its derivatives are aromatic since they possess a hexatriene ring system similar to that in benzene. The aromaticity of furan, thiophene, and pyrrole is ascribed to resonance.

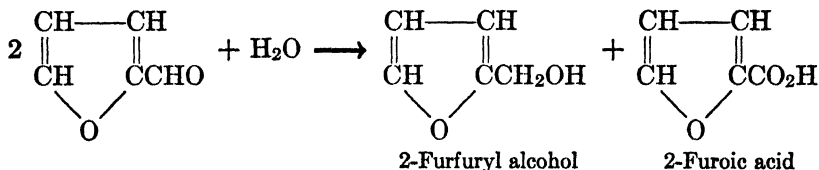
**Furan.** Furan is relatively rare but several of its derivatives are widely used. Furfural is the most important of these. It is now manufactured on a large scale from oat hulls (p. 293) and is used extensively as an



extraction liquid in petroleum refining. It is very much like benzaldehyde in its reactions. For example, it undergoes the benzoin condensation to give furoin.

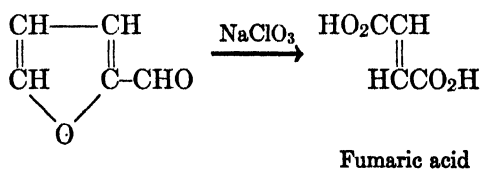


Similarly, the Cannizzaro reaction converts it into 2-furfuryl alcohol and 2-furoic acid (the usual method of naming heterocyclic compounds is by reference to number systems in which the hetero atom is numbered 1).

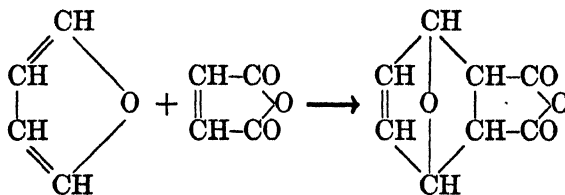


Furan and its derivatives undergo nuclear substitution.

An interesting and useful transformation of furfural is its conversion to fumaric acid by oxidation with sodium chlorate.

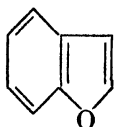


The presence of a diene system in the furan molecule is indicated by the fact that it undergoes a typical diene condensation with maleic anhydride.

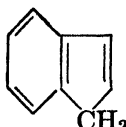


Coumarone or benzofuran is found in coal tar along with indene, which it resembles in some respects. Although fairly stable to alkalis and ammonia, coumarone is resinified by sulfuric acid. Valuable commercial

resins are obtained by polymerizing the crude mixture of coumarone and indene.



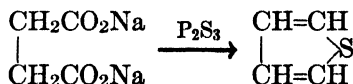
Coumarone



Indene

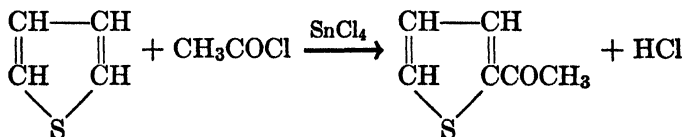
**Thiophene.** If close similarity to benzene is taken as a criterion of aromaticity, thiophene is very aromatic indeed. For although benzene from coal tar contains about 0.5 per cent of thiophene this contaminant passed unnoticed for nearly sixty years after benzene became known. Indeed up to the year 1883 the indophenin test was used to detect benzene—a test which is not given by benzene at all but by thiophene. Victor Meyer, in a popular lecture on benzene, prepared the hydrocarbon by decarboxylation of benzoic acid. To prove the identity of the product he used the test—isatin and sulfuric acid—but to his surprise the expected blue color was not observed. Subsequent work disclosed the presence of thiophene in coal tar benzene and showed that it was responsible for the color test so long incorrectly ascribed to benzene.

Thiophene is prepared by treating sodium succinate with phosphorus trisulfide.



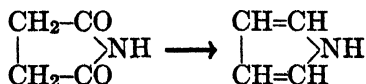
It readily undergoes nitration and sulfonation. In fact, sulfonation takes place more rapidly than with benzene—a fact which is used in freeing benzene from thiophene. This process consists in shaking the impure benzene with sulfuric acid.

A good yield of 2-acetothienone is obtained by treating thiophene with acetyl chloride in the presence of stannic chloride.

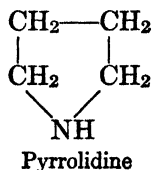
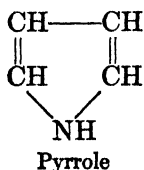


Methylthiophenes, like toluene, can be oxidized to the corresponding carboxylic acids. The nucleus is not attacked.

**Pyrrole.** Pyrrole occurs in coal tar and bone oil and can be made by distilling succinimide with zinc dust.



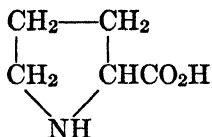
Pyrrole boils at  $129^\circ$ , is sparingly soluble in water and has very weakly basic properties. The latter characteristic is interesting when contrasted with the strongly basic character of pyrrolidine, the reduction product of pyrrole.



Interesting also is the fact that pyrrolidine is water-soluble whereas pyrrole is not. Pyrrole imparts a red color to pine wood shavings in the presence of hydrochloric acid. This serves as a test for its presence.

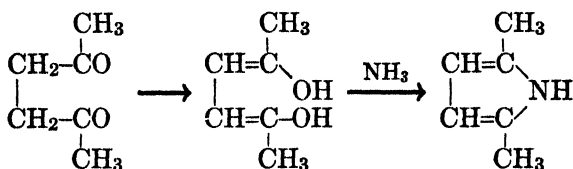
Pyrrole is the principal building block in the construction of certain pigments such as hemoglobin of the blood and chlorophyll of plants.

Among the many pyrrolidine derivatives found in nature is proline or 2-pyrrolidinecarboxylic acid.

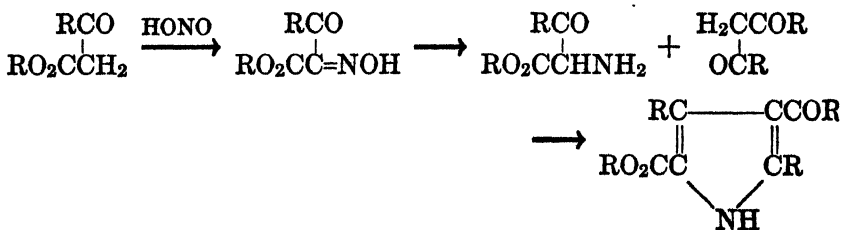


It is a product of hydrolysis of most proteins.

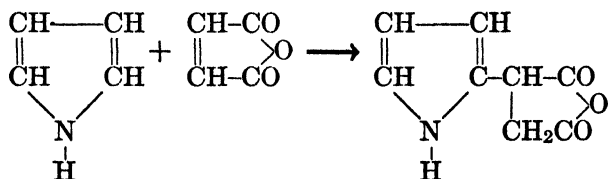
Dimethylpyrrole is formed from acetonylacetone and ammonia.



This synthesis, due to Knorr, is general for  $\gamma$ -diketones. A more useful method likewise due to Knorr involves the condensation of an amino ketone with a ketone or 1,3-diketone. The amino ketone is made by reducing the corresponding oxime and is used without being isolated. An example is the following:

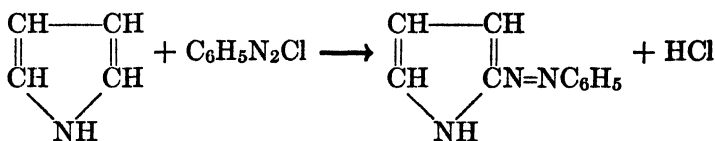


Pyrrole appears to contain a typical butadiene system, but unlike furan it does not undergo the diene reaction with maleic anhydride. The reaction is one of simple addition.

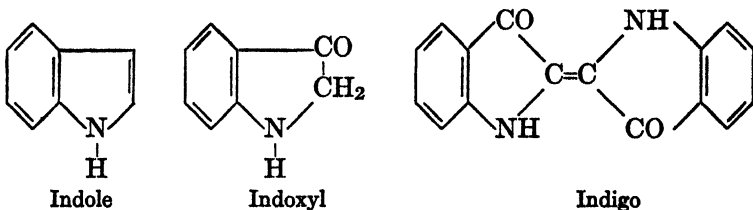


In acid solution pyrrole seems to lose its aromatic character and undergoes polymerization in much the same manner as does cyclopentadiene.

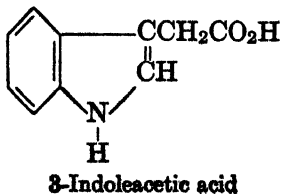
Pyrrole couples with diazonium salts to give azo compounds.



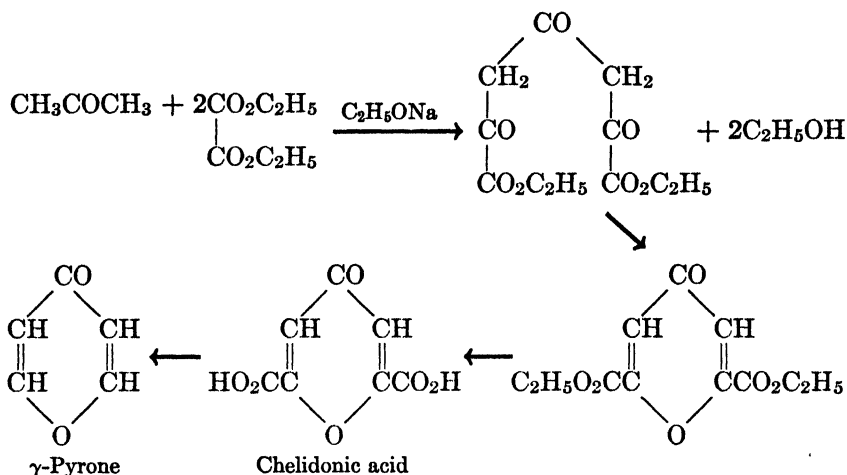
*Indole* is benzopyrrole and is the parent substance of indigo. Indigo occurs in the plant as the glucoside of indoxyl. Air oxidation of indoxyl gives indigo.



3-Indoleacetic acid has been shown to possess the properties of auxins and is known as heteroauxin. Auxins regulate the growth of plants and determine their behavior with respect to growing away from the ground and toward the light.



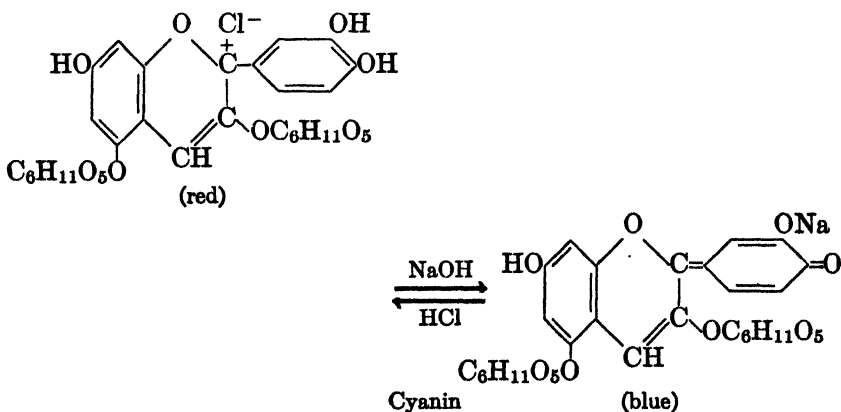
**$\gamma$ -Pyrones.**  $\gamma$ -Pyrone can be made from acetone and ethyl oxalate.



If ethyl acetoacetate and phosgene are used, 2,6-dimethyl- $\gamma$ -pyrone results.

The most remarkable property of the  $\gamma$ -pyrones is the ability to form oxonium salts with acids.\* The exact structure of these salts has not been established.

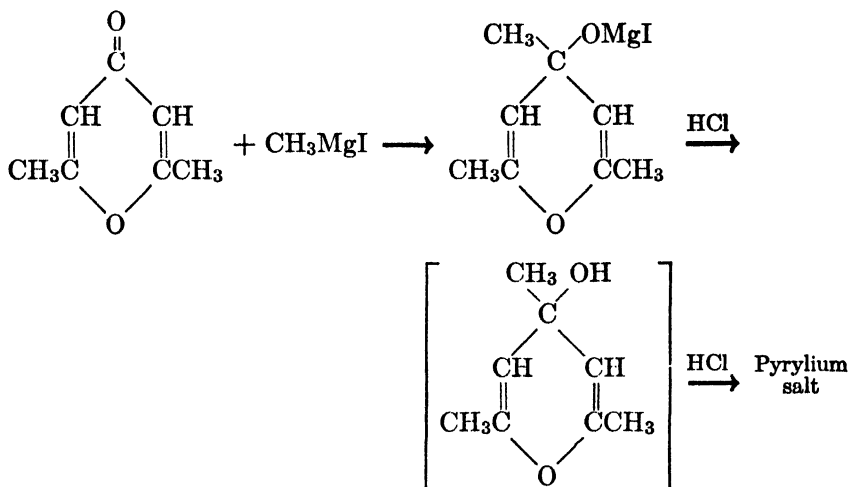
**Pyrylium Salts.** These salts occur in nature and are responsible for the colors of certain flowers. The colored materials are known as anthocyanidins and in the plant are combined with one or more molecules of sugar. An example is **cyanin** which is responsible for the red color of roses and the blue color of the corn flower.



\* It must not be thought that the formation of oxonium compounds is rare in organic chemistry. However, only in isolated cases have they proved to be stable

The color is a function of  $pH$ ; this explains why the same pigment gives a blue color to one flower and a red color to another.

A simple pyrylium salt may be prepared from dimethylpyrone by the following reactions:



**Pyridine.** Pyridine is an unpleasant-smelling liquid, boiling point  $116^\circ$ , found in coal tar. It is a weak base and is soluble in water. Its outstanding property is its inertness. Strong oxidizing agents such as chromic oxide do not attack it and it is brominated, nitrated, or sulfonated only with great difficulty. The relative ease with which rings are alkylated and acylated by the Friedel-Crafts method places them in the following order of decreasing reactivity: pyrrole, furan, thiophene, anthracene, naphthalene, benzene, cyclohexene, cyclohexane, and pyridine.

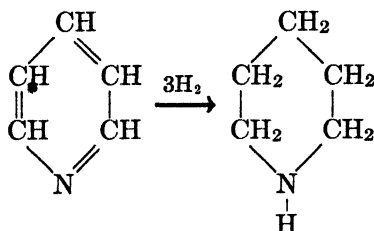
Pyridine has been compared with nitrobenzene because it undergoes substitution with about the same order of difficulty. For example, neither will undergo the Friedel-Crafts condensation. The comparison can be carried further for in  $\alpha$ - and  $\gamma$ -chloropyridines as in *o*- or *p*-chloronitrobenzene the halogen atom is reactive. For example, it can be replaced by a phenylamino group by treatment of the chloropyridine with aniline. Similarly  $\alpha$ - and  $\gamma$ -picolines, like *o*- and *p*-nitrotoluenes, have active methyl groups.

under ordinary conditions. It is highly probable that oxonium salt formation is involved in the conversion of alcohols to alkyl halides by the action of hydrogen halides.

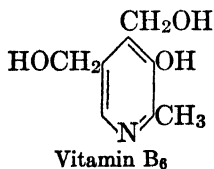


These oxonium salts frequently have been isolated; those from highly branched alcohols such as diisopropylcarbinol seem to be most stable.

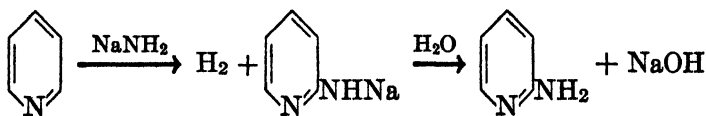
Hydrogenation transforms pyridine to piperidine.



Vitamin B<sub>6</sub> or pyridoxine is the factor of vitamin B which prevents or cures a type of dermatitis produced in young rats by a diet in which the only vitamin B components present are purified thiamin and riboflavin. It has been shown to be a derivative of pyridine having the following formula:

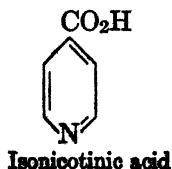
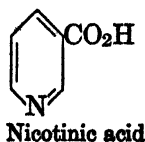
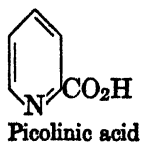


Nitration of pyridine can be effected only at high temperatures; 3-nitropyridine is formed. Amino pyridines are prepared by the action of ammonia on  $\alpha$ - and  $\gamma$ -chloropyridines. All three aminopyridines have been made by the Hofmann hypobromite degradation of the corresponding amides.  $\alpha$ -Aminopyridine is conveniently prepared by the action of sodium amide on pyridine.



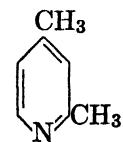
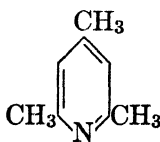
The  $\alpha$ - and  $\gamma$ -aminopyridines differ from the  $\beta$ -isomer in that they can be diazotized only with difficulty. The diazonium salts cannot be isolated. In water they decompose to give the corresponding hydroxypyridines.

*Picolines* are methylpyridines. Oxidation converts them to the corresponding carboxylic acids—picolinic, nicotinic, and isonicotinic acids.

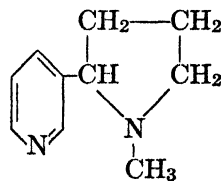


Nicotinic acid is one of the vitamins of the B group. It is the pellagra-preventive factor and is found in liver, muscle meats, fish, milk, green vegetables, and yeast.

*Lutidines* are dimethylpyridines and *collidines* are trimethylpyridines. Although pyridine is water-soluble and very hygroscopic, its homologs become increasingly less soluble with increase in molecular weight. Many of them are more soluble in cold than in hot water—a typical property of tertiary amines. The most striking example is nicotine. Below 60° and above 210° it is soluble in water in all proportions, but between these temperatures it is only partly miscible.

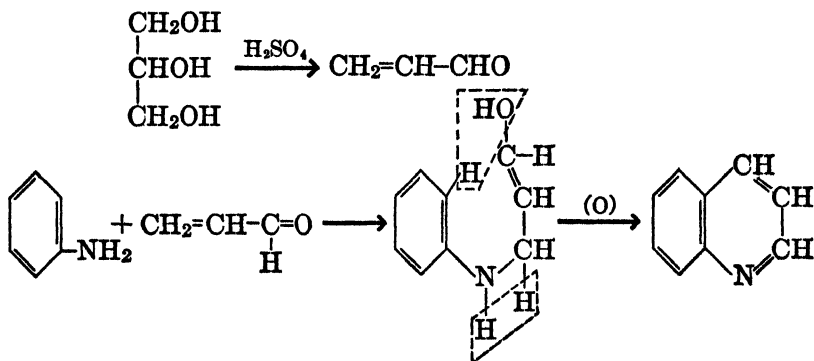
 $\alpha,\gamma$ -Lutidine

Collidine

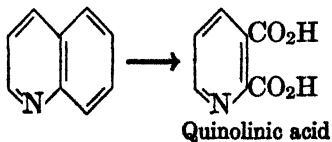


Nicotine

*Quinoline* is benzopyridine. It occurs in coal tar and bone oil. It is most conveniently made by the Skraup synthesis, which involves the condensation of aniline with glycerol in the presence of sulfuric acid and nitrobenzene. In all probability the mechanism is the following:

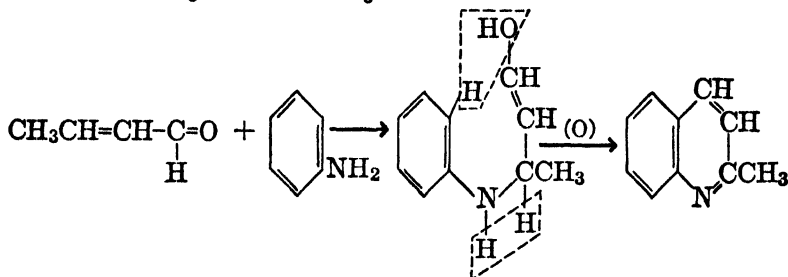
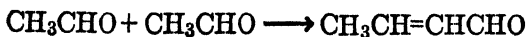


The great stability of the pyridine ring to oxidizing agents is shown by the fact that oxidation of quinoline destroys the benzene ring preferentially, yielding quinolinic acid.

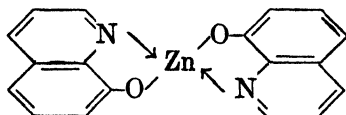




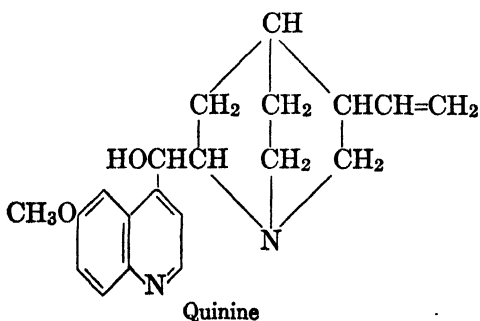
Quinaldine is made by heating aniline with acetaldehyde in the form of paraldehyde. The mechanism is probably similar to that proposed for the Skraup synthesis.



8-Hydroxyquinoline, known as "oxine," is used in the separation of certain metals with which it forms insoluble chelate derivatives. Chief of these are aluminum, magnesium, and zinc. The zinc compound, for example, has the following structure:

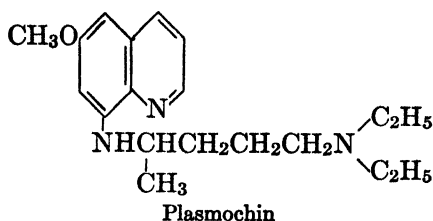


Many quinoline derivatives possess marked physiological activity and certain of them are important drugs. The alkaloid, quinine, belongs to this group. It is used in the treatment of malaria.

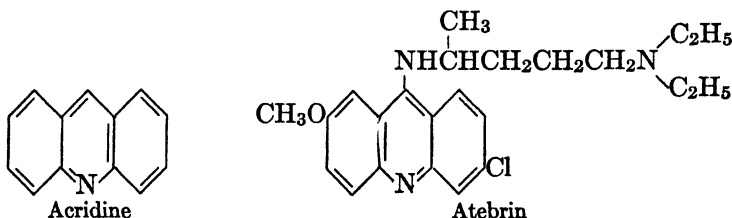


There are two functional phases of the malarial parasite, the schizonts (which cause the fever) and the sexual forms or gametocytes (which spread the disease). Quinine is effective only against the former.

Intensive research has developed useful synthetic anti-malarials of which plasmochin and atebrin are the most important. Plasmochin is a quinoline derivative with a complex side chain.



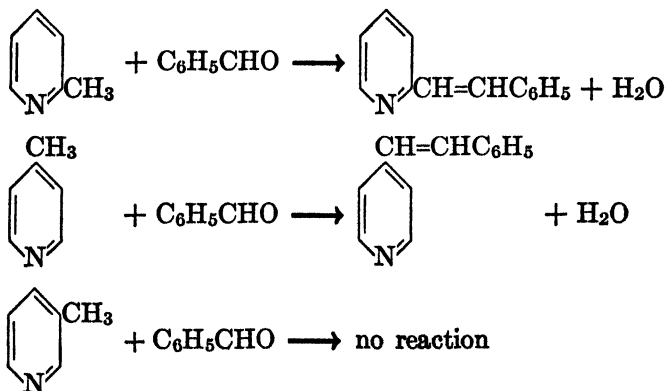
It is the only drug that attacks gametocytes and is used along with quinine to prevent spread of the disease. Atebrin is a schizonticidal drug. It is derived from acridine, a benzolog of quinoline.



Isoquinoline is isomeric with quinoline and occurs in coal tar.

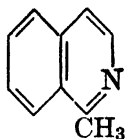


**Side-Chain Activation in the Pyridine Series and in Related Compounds.** It was observed long ago that certain methylpyridines were capable of undergoing the reactions of compounds containing active methyl groups. For example,  $\alpha$ - and  $\gamma$ -picolines react with benzaldehyde to give benzal derivatives. The  $\beta$ -isomer will not do this.

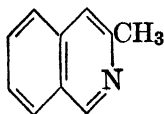


Evidently the  $>C=N-$  grouping activates the methyl group attached to it as in  $\alpha$ -picoline, i.e., the group  $CH_3C=N-$  has essentially the properties of the corresponding methyl ketone,  $CH_3C=O$ . By reference to the principle of vinylogy it is clear that the  $\gamma$ - but not the  $\beta$ -isomer would share this property.

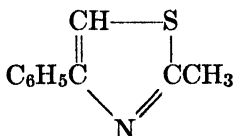
Similar reasoning shows why 1-methylisoquinoline has an active methyl group whereas the 3-isomer has not. Also 2-methyl-4-phenylthiazole has an active methyl group whereas its isomer, 2-phenyl-4-methylthiazole, does not.



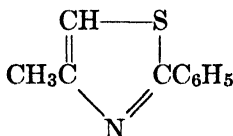
1-Methylisoquinoline



3-Methylisoquinoline



2-Methyl-4-phenylthiazole



2-Phenyl-4-methylthiazole

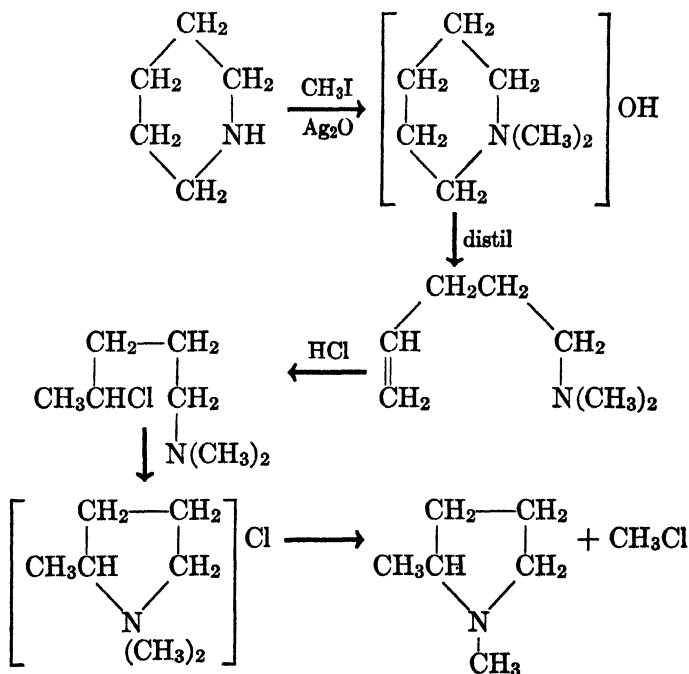
**Alkaloids.** Alkaloids are naturally occurring basic organic nitrogen compounds. The term is generally limited to include only those of plant origin. Alkaloids are usually optically active and have marked physiological activity. With few exceptions they contain at least one nitrogen atom linked in a cyclic structure. These substances are found almost exclusively in seed-bearing plants, chiefly in dicotyledons. The view is commonly held that they are by-products of plant metabolism.

It is an interesting fact that in alkaloids which have an alkyl group attached to a nitrogen or oxygen atom this group is nearly always methyl. This has been interpreted as support for the theory that formaldehyde is involved in plant synthesis. Pyridine, pyrrole, quinoline, and isoquinoline rings are of frequent occurrence, generally in reduced form.

For the determination of structure of alkaloids several general procedures are available. Methoxyl groups are determined by Zeisel's method. Methyl groups on nitrogen are split off by heating the alkaloid hydroiodide at  $200-300^\circ$ . It is a general rule that thermal decomposition of quaternary ammonium halides gives a methyl halide if a methyl group is attached to the nitrogen atom.

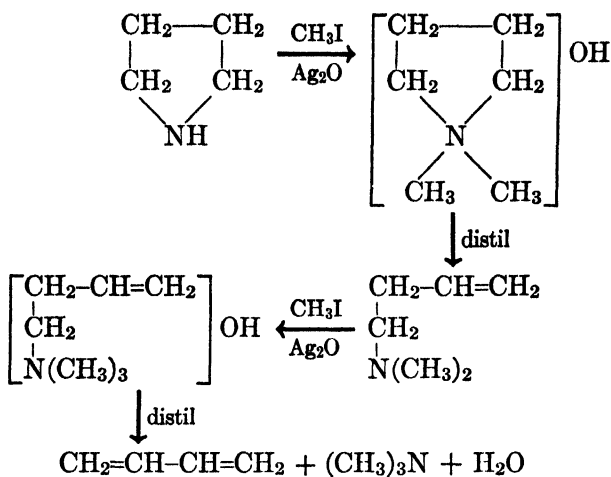
**The Degradation of Nitrogen Bases.** Hofmann's celebrated method has already been mentioned. However, no discussion of alkaloids is complete without reference to this powerful tool. Primary amines react with methyl halides to give secondary amines which in turn yield tertiary amines, and these by addition give quaternary ammonium halides. This is properly known as "exhaustive methylation." The bases corresponding to the quaternary ammonium salts generally decompose when heated and give a tertiary amine and an olefin. The ethyl radical is the one which is most easily split off.

An interesting application of Hofmann's method is found in the transformation of piperidine into *N*, $\alpha$ -dimethylpyrrolidine.

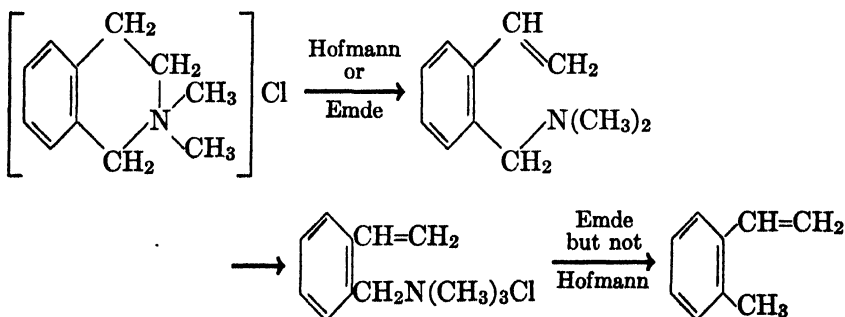


Here again use is made of the fact that the methyl group can be eliminated preferentially by thermal decomposition of the quaternary ammonium halide containing it.

Pyrrolidine itself yields butadiene when subjected to exhaustive methylation.

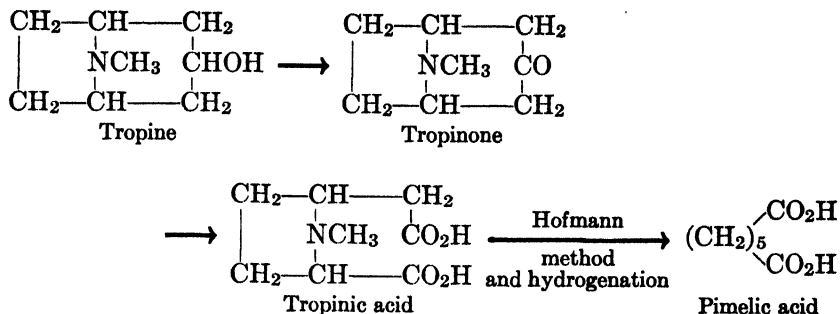


The Hofmann degradation fails with unhydrogenated pyridine, quinoline, and isoquinoline rings and with hydrogenated quinolines. Useful modifications due to Emde involve reduction of the quaternary ammonium halide with sodium amalgam or hydrogen and a catalyst. An example follows.



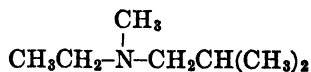
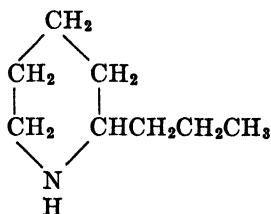
The failure of exhaustive methylation when applied to heterocyclic bases such as pyridine is due to the rearrangement of the quaternary hydroxides.

Oxidation is a useful tool also. The following transformations of tropine (from atropine) illustrate its value. Gentle oxidation gives tropinone. The latter yields a dibenzal derivative and must have two  $\text{CH}_2$  groups adjacent to the ketone group. Vigorous oxidation converts tropinone to tropinic acid, which can be converted to pimelic acid.



## PROBLEMS

1. Indicate a method of converting furfural to furil. What would happen if furil were heated with a strong alkali?
2. Compare the chemical properties of pyridine with those of nitrobenzene.
3. Apply the Hofmann degradation method to the following bases:



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## CHAPTER XXXIV

### SYNTHETIC DYES FROM COAL TAR

**History.** A dye is a colored substance which can be made to adhere to fabrics such as cotton, silk, or linen. The use of dyestuffs to impart color to fabrics was practiced by the ancients and was known to the most primitive peoples. Nearly all the early dyes were of vegetable origin, indigo and alizarin being the best-known examples.

Alizarin was obtained from the madder plant and used to produce Turkey red. Indigo likewise came from a plant, and up to the latter part of the nineteenth century large areas of land were devoted to the production of these plants.

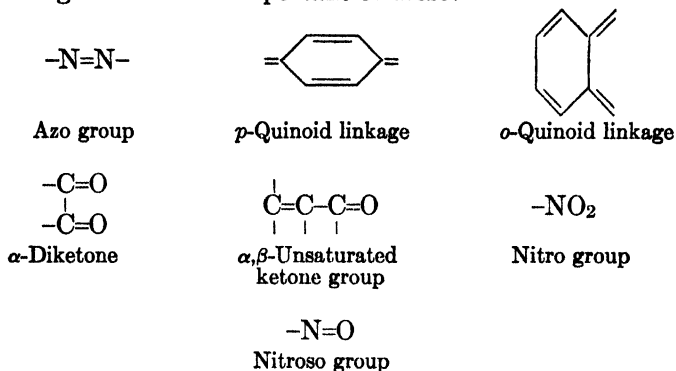
Nearly all dyes now in use are derivatives of benzene and other coal tar products—hence coal tar dyes—and it is not surprising that very little was known about them up to 1865, the date of Kekulé's announcement of the structure of benzene. As a matter of fact the first synthetic dye was made nine years before by Perkin who was trying to convert aniline—then of unknown constitution—to quinine by oxidation. He obtained a substance whose beautiful violet solution dyed silk and wool. It was named *mauve* and proved later to be a triphenylmethane derivative.

This dye and similar ones were put on the market almost immediately, and from that time forward synthetic dyes rapidly crowded the natural dyestuffs from the market. Graebe and Liebermann worked out the structure of alizarin in 1868, and within a few years the synthetic dye displaced that obtained from the madder. Similarly in 1882 Baeyer elucidated the structure of indigo and in the course of time synthetic indigo replaced the natural form.

The famous Tyrian purple prized by the Romans 2000 years ago was obtained from certain shell fish in the Mediterranean Sea. It has recently been shown to be a dibromo derivative of indigo and is not now manufactured because similar shades can be produced by other dyes which are manufactured more cheaply.

**Color and Chemical Constitution.** All organic compounds absorb light but the absorbed light usually lies beyond the visible portion of the spectrum. Hence we say the compounds are colorless. Experience has

shown that unsaturated compounds are more likely to be colored than saturated compounds. Certain unsaturated groups are definitely associated with color and are known as *chromophoric groups* or *chromophores*. The following are the most important of these:



The presence of one or more aryl groups attached to the chromophore is usually necessary.

A substance containing a chromophore is a *chromogen*. However, in order to be a dye a chromogen must contain a second group—known as an *auxochrome group*—which renders the color more intense and gives the chromogen an acidic or basic character so that it will adhere to the fabric. The most effective auxochrome groups are  $\text{-OH}$ ,  $\text{-NH}_2$ ,  $\text{-NHR}$ ,  $\text{-NR}_2$ , and  $\text{-CO}_2\text{H}$ . The sulfonic acid group is of value not only as an auxochrome group but also is often used to render the dye water-soluble.

**The Classification of Dyes According to Use.** Dyes are classified not only according to their structures but also after the manner in which they are used. On the latter basis they are classed as direct dyes, mordant dyes, ingrain or developed dyes, vat dyes, and sulfur dyes.

A *direct dye* is dissolved in water as its sodium salt if *acidic* and as its hydrochloride if *basic*. The fabric is then dyed by immersion in the hot aqueous solution. Cotton fabrics are more difficult to dye in this manner than are textiles derived from animal fibers. Most direct dyes are used only with animal fibers.

Since proteins are amphoteric it is presumed that they tend to hold acidic and basic dyes through salt formation. However, this theory leaves much to be desired and cannot be applied to cotton dyeing.

Direct dyes for cotton—called substantive dyes—nearly always have two azo groups. An example is Congo red, to be described later.

*Mordant dyes* require the use of mordants such as the hydroxides or basic salts of aluminum, iron, or chromium. The fabric is first impregnated with the mordant and then dipped in a solution of the dye. The



mordant is generally put on the fabric in the form of the water-soluble acetate or formate and then subjected to treatment with steam. This hydrolyzes the salt to the metal hydroxide. When certain dyes are precipitated by such mordants an insoluble, colored substance results to which the name *lake* has been given. The use of a mordant dye involves the formation of such a lake in the fibers of the cloth. The function of the mordant will be discussed more fully in the sequel.

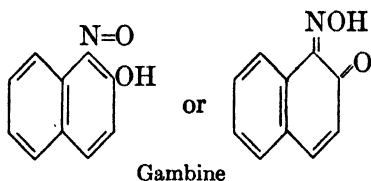
3. *Ingrain or developed dyes.* These dyes are insoluble and are produced in the cloth by the interaction of suitable substances. Thus if a cloth is dipped successively in a solution of a naphthol and a diazonium solution an azo dye is formed.

4. *Vat dyes* such as indigo are insoluble but can be reduced to a soluble form by the action of sodium hydrosulfite ( $\text{Na}_2\text{S}_2\text{O}_4$ ). The soluble form is placed on the cloth and subsequently reoxidized to the insoluble dye.

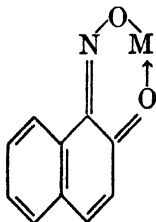
5. *Sulfur dyes* are produced by heating phenols or anilines with sulfur or a metal polysulfide. They are reduced by sodium sulfite. The fabric, after being immersed in the resulting solution, is exposed to air which slowly reoxidizes the dye to the colored form. This process is essentially that used with vat dyes.

**The Classification of Dyes According to Structure.** A clearer idea of the great variety of dyes may be obtained by considering typical examples from the standpoint of structure. A few of these are listed here according to structural types.

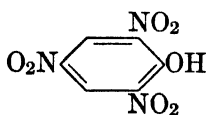
1. *Nitroso.* The nitroso group imparts a green color to the molecule even in the aliphatic series. An example of a nitroso dye is *gambine*.



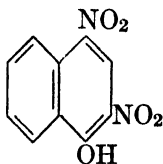
Mordanted with ferric chloride it dyes cotton a fast green. The function of the mordant is probably to form an insoluble chelate derivative.



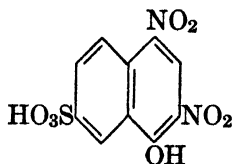
2. *Nitro*. *Picric acid* illustrates this type. It dyes silk and wool yellow but the color is fugitive.



Picric acid



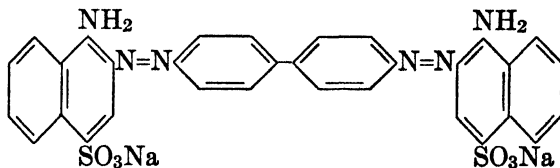
Naphthol yellow



Naphthol yellow S

Naphthol yellow and naphthol yellow S are similar in type.

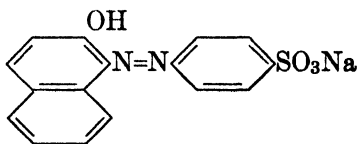
3. *Azo dyes*. These dyes are made by coupling a diazonium salt with an amine or phenol. An example is Congo red, which is derived from benzidine and naphthionic acid.



Congo red

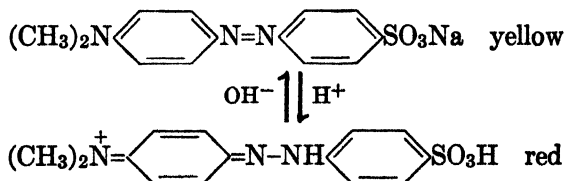
This dye is direct to cotton. However, it turns blue when treated with a strong acid and for this reason is not a satisfactory dye.

*Orange II* is obtained from sulfanilic acid and  $\beta$ -naphthol.

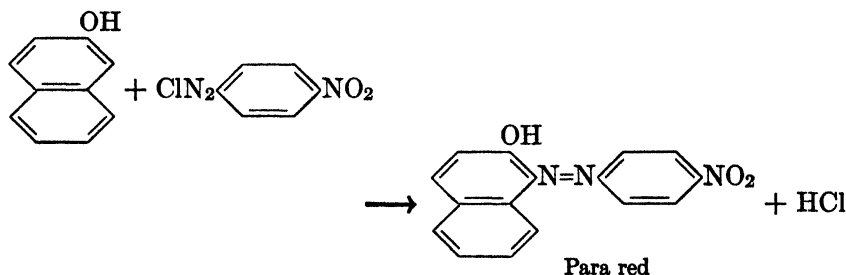


Orange II

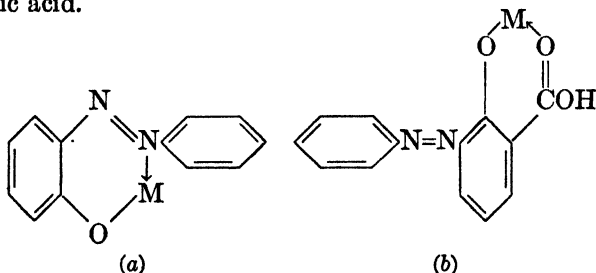
*Methyl orange* is really not a dye but an indicator. Its color change is interesting since it involves a change of chromophore. The yellow form owes its color to the azo group, the red to the paraquinoid group.



*Para red* is a good example of a developed dye. The cloth is passed successively through solutions of  $\beta$ -naphthol, diazotized *p*-nitroaniline, and sodium acetate. The sodium acetate lowers the pH so that coupling will take place.

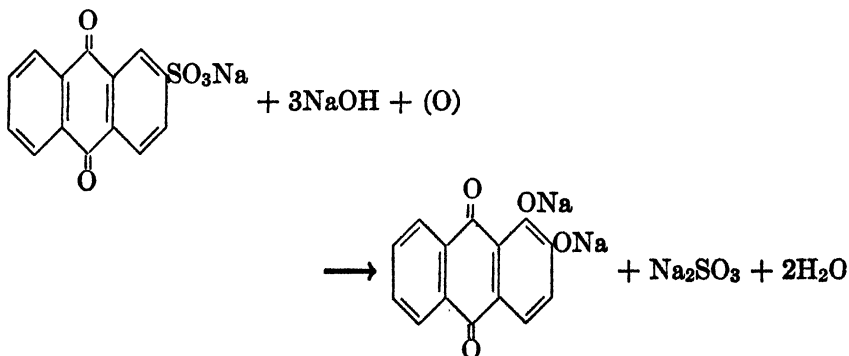


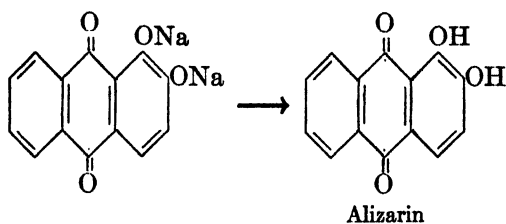
Nearly all the azo dyes of known constitution which can be mordanted with salts of polyvalent metals contain a replaceable hydrogen atom and a donor atom so situated as to permit chelation. It is well known that of this group those which are mordant dyes either (a) have a hydroxy group in a position *ortho* to the chromophore group or (b) are derivatives of salicylic acid.



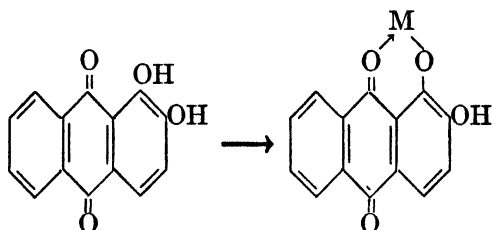
In the light of recent studies it may be taken as proved that the power of dyeing fabrics conferred upon a dye by metal salts is evidence that the dye is capable of forming a chelate ring involving the metal atom.

4. *Anthraquinone dyes.* *Alizarin* belongs to this group. It is manufactured by fusing sodium anthraquinone- $\beta$ -sulfonate with sodium hydroxide to which chlorate has been added. This gives the sodium salt from which alizarin is obtained by treatment with acids.

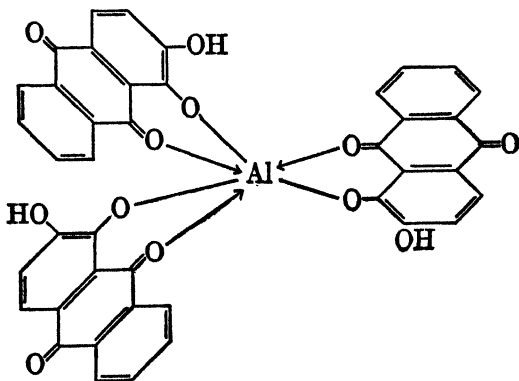




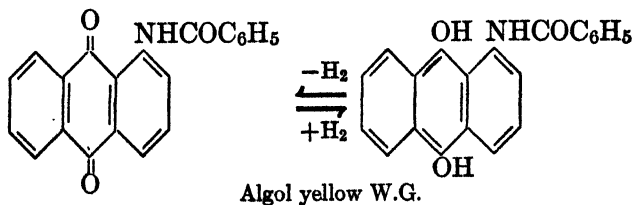
Alizarin is used with a mordant; usually salts of iron, chromium, tin, or aluminum are employed. The latter gives Turkey red, much used for dyeing cotton. In this connection it is significant that all anthraquinone dyes which can be mordanted have a hydroxyl group in position 1. This is taken to mean that the mordant functions by chelate ring formation.



The formula for Turkey red involves three molecules of alizarin.

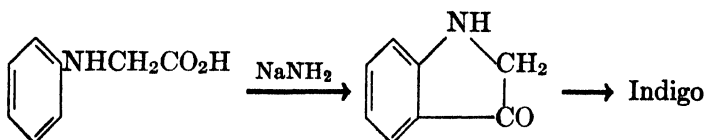


However, the more important anthraquinone dyes are vat dyes. This type is illustrated by *algol yellow W.G.*

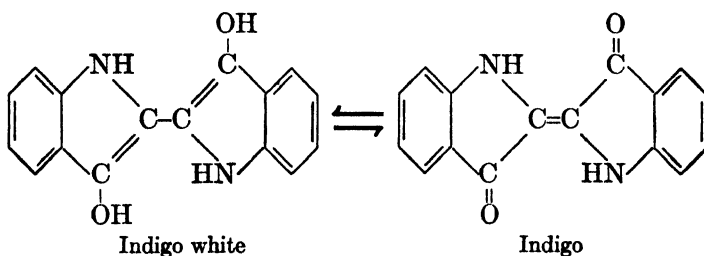




A simpler and now more important synthesis is the following.

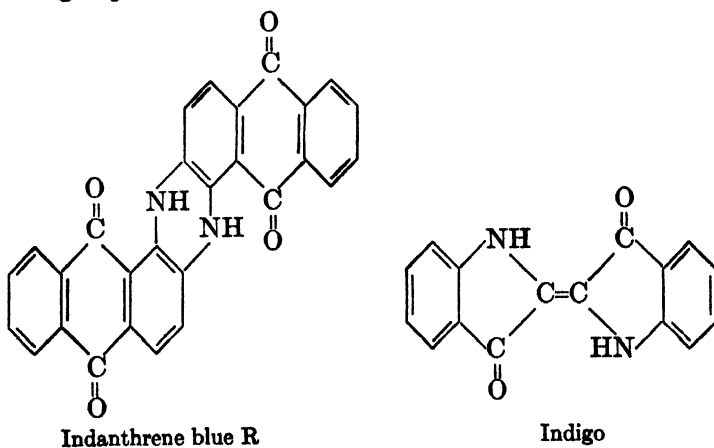


The chromophore of indigo is  $\text{O}=\text{C}-\text{C}=\text{C}-\text{C}=\text{O}$ . Reduction with sodium hydrosulfite converts the dye to a colorless alkali-soluble form known as indigo white. Oxidation by the air converts indigo white to indigo.

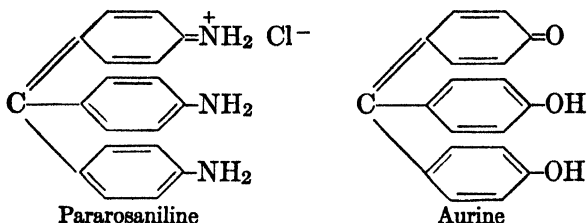


X-ray studies show that indigo has a center of symmetry and hence must be the *trans* form. The *cis* modification is not known. The stability of the *trans* form is probably due to hydrogen bonding.

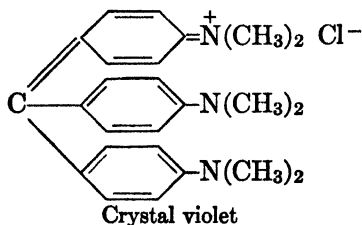
The structure of indigo which Baeyer established in 1882 is strongly supported by the behavior of analogously constituted substances; an example is indanthrene blue R. In both this dye and indigo the chromophore group,  $\text{O}=\text{C}-\text{C}=\text{C}-\text{C}=\text{O}$ , is joined to a benzene ring which holds an imino group.



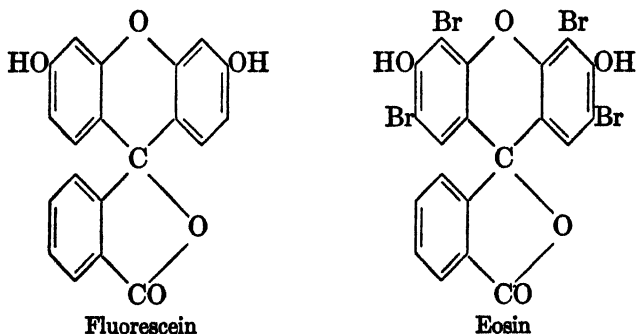
6. *Triphenylmethane dyes*. These dyes have the type of structure illustrated by the following; the chromophore group is the quinoid nucleus.



From Michler's ketone and dimethylaniline is obtained hexamethyl-pararosaniline or *crystal violet*. The substitution of methyl groups for the six amino hydrogen atoms in pararosaniline changes the shade from red to violet. Resonance would permit each ring in turn to assume the quinoid form and is supposed to enhance the color.



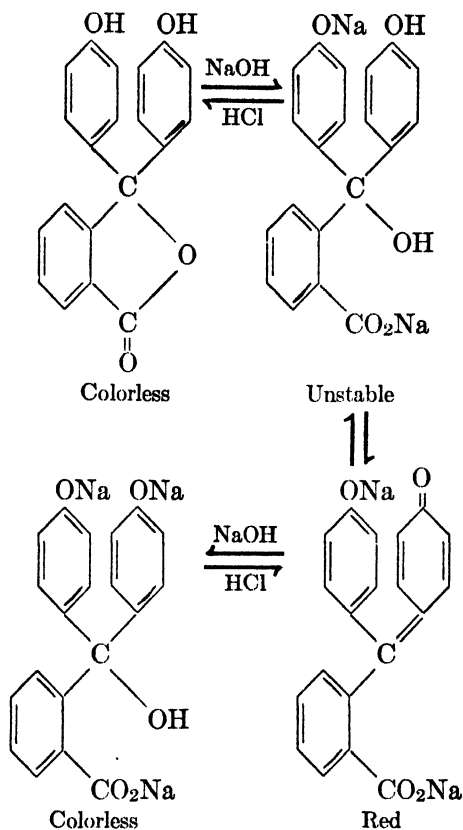
7. *Pyronine dyes*. From phthalic anhydride are obtained fluorescein, eosin, and similarly constituted dyes. These are known as pyronine dyes.



Eosin is used in red inks. The colored form of a pyronine dye is illustrated by the formula of mercurochrome (p. 431), which is a disinfectant belonging to this group.

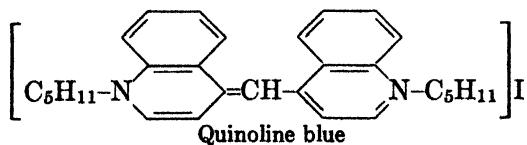
Although not a true pyronine dye, phenolphthalein is very closely

related to this group. The color changes of phenolphthalein are explained as indicated below.



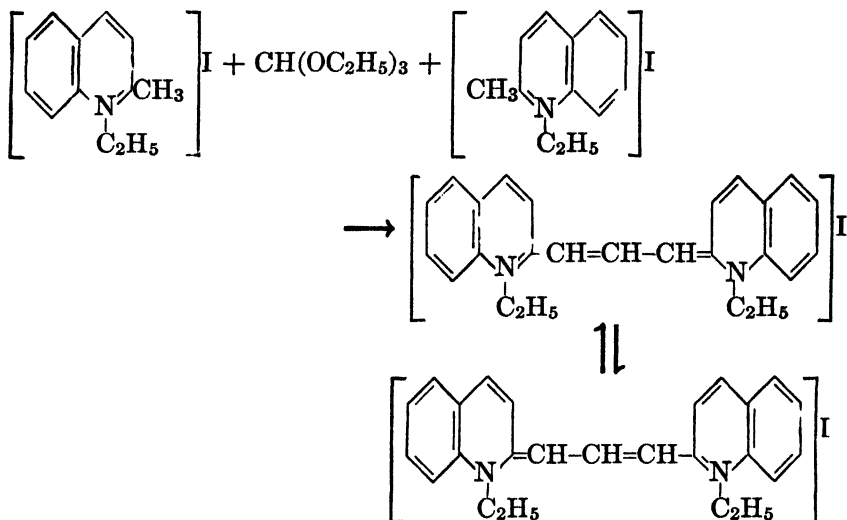
8. *Cyanine dyes.* Recently attention has been focused on the cyanine dyes because they are capable of functioning as photographic sensitizers. Ordinary silver halide photographic plates are sensitive only to the violet and blue regions of the spectrum, but by adding suitable cyanine dyes to the liquid emulsion the plates may be rendered remarkably sensitive to green, yellow, orange, and red.

The essential structural feature of these dyes is formed by two nitrogen atoms—one trivalent and the other tetravalent—joined together by a conjugated system of single and double bonds. An example is quinoline blue.



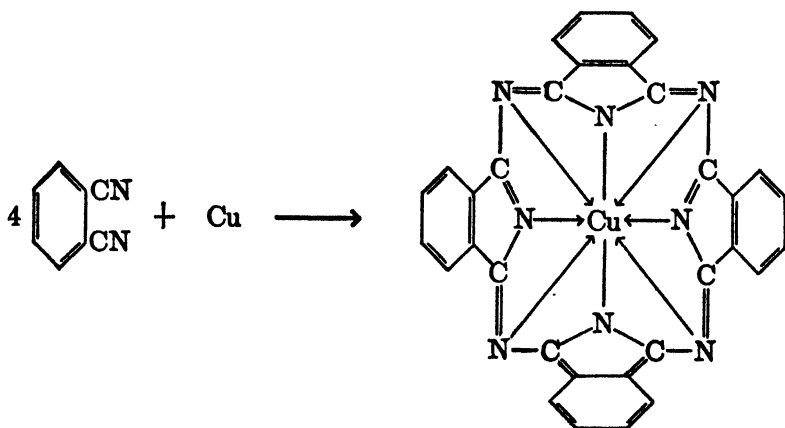


A similar dye, pinacyanole, is made by condensing quinaldine ethiodide and ethyl orthoformate.



The possibility of resonance between the two forms is necessary if the compound is to be a dye.

9. *Phthalocyanine dyes.* One of the most interesting and valuable types of chromophores is that in phthalocyanine and its metal derivatives. Copper phthalocyanine may be taken as an example of the latter. It is formed by treating *o*-phthalonitrile with copper and has a complex structure similar to those of chlorophyll and hemin.



Many other similar metal derivatives have been made. These are fast blue or green pigments characterized by remarkable stability toward

acids, bases, and heat. They are employed in practically every field in which colored pigments are of use.

The evidence supporting the structure given for these pigments is based largely on x-ray data. Presumably the formula given is but one of several resonance hybrids; in the sixteen-membered ring the atoms show a spacing which indicates a resonating structure.

### PROBLEMS

1. Suggest a reason for the observation that unsaturated compounds are more likely to be colored than are saturated compounds.
2. How can the function of mordants be explained by use of the electronic theory of valence?
3. What properties must a compound possess to be useful as an indicator?

### SUGGESTED READINGS

- FIESER, "The Discovery of Synthetic Alizarin," *J. Chem. Education*, **7**, 2609 (1930).  
LEWIS and CALVIN, "The Color of Organic Substances," *Chem. Rev.*, **25**, 273 (1939).  
DOJA, "Cyanine Dyes," *Chem. Rev.*, **11**, 273 (1932).  
DAHLEN, "The Phthalocyanines, A New Class of Synthetic Pigments and Dyes," *Ind. Eng. Chem.*, **31**, 839 (1939).



## APPENDIX A

### Notes on Nomenclature and Pronunciation

**Nomenclature.** The continual increase in the variety and complexity of organic compounds has required constant revision of our systems of nomenclature. The American organic chemist's authoritative reference in the matter is the index of the current volume of Chemical Abstracts. It is especially to be noted, however, that only *the indexes* of Chemical Abstracts may be depended on to use the accepted names.

The Chemical Abstracts system of naming is designed frankly for indexing purposes and is often too cumbersome for use in speaking or writing. It is based, of course, on the Geneva system of naming. This system was revised in 1933. (A very useful book on the naming of ring compounds is also available.)

Although a standard system for naming compounds now exists, chemists often continue to use more than one name for a given substance. This may appear to be undesirable, but it has the great practical advantage of permitting the names to vary with the context. This possibility of option often makes it easier to bring out analogies and frequently makes for clearer exposition.

It is only *in connection with indexing* that chemists are expected to adhere to the Chemical Abstracts system. For other purposes it cannot be said *a priori* that one name is preferable to another. The choice is often determined by the context. In fact, situations may arise in which it is warrantable to discard all the known names and coin a new one.

Consider the compound whose structural formula is  $\text{C}_6\text{H}_5\text{COCH}_2\text{CN}$ . In a discussion of nitriles it might well be described as *benzoylacetoneitrile*. This is the name used by Chemical Abstracts. If the topic under consideration is cyanides, *phenacyl cyanide* would probably be the most appropriate name. Regarded as a derivative of acetophenone it is  *$\omega$ -cyanoacetophenone*.

Whether one says *n*-butyl alcohol or 1-butanol might very well depend on whether the compound is being related, for example, to cetyl alcohol or to 1-hexadecanol. A comparison of cetyl alcohol with *n*-butyl alcohol seems a little more appropriate than one between cetyl alcohol and 1-butanol; the use of the latter names together is undesirable since they fail to suggest the structural relationship which exists between the compounds.

Finally, it should be said that most chemists find it impracticable to achieve a complete mastery of the Chemical Abstracts system as applied to very complex molecules. Generally they are able to name a new compound correctly by analogy with similar names already in the Chemical Abstracts index. In difficult cases specialists must be consulted.

**Pronunciation.** The American pronunciation of chemical words shows a great lack of uniformity. This appears to be due in part to the fact that many Americans studied abroad and acquired foreign pronunciations. Many, too, have made the acquaintance of new words through reading and in some instances have never heard them pronounced.

Efforts have been initiated to improve the situation. A few years ago a survey was made as to the pronunciation of a selected list of chemical words and the results were published.

This report lists a large number of chemical names and indicates the pronunciations which are most used. Also, there are indications as to which pronunciations seem preferable from a consideration of general trends in American speech.

#### REFERENCES

1. PATTERSON, "Definitive Report of the Commission on the Reform of the Nomenclature of Organic Chemistry," *J. Am. Chem. Soc.*, **55**, 3905 (1933).
2. PATTERSON, *The Ring Index*, Reinhold Publishing Corporation, New York, 1940.
3. "The Pronunciation of Chemical Words," *Ind. Eng. Chem., News Ed.*, **12**, 202 (1934).

## APPENDIX B

### Problems and Questions for Review

I. Show how the following concepts are used to explain the properties of organic molecules:

- |                             |                       |
|-----------------------------|-----------------------|
| 1. Resonance                | 6. Tautomerism        |
| 2. Chelation                | 7. Mills-Nixon effect |
| 3. Parachor                 | 8. Vinylogy           |
| 4. Coordinate covalent bond | 9. Strain             |
| 5. Hydrogen bond            | 10. Steric hindrance  |

II. Illustrate the following types of reactions:

- |   |   |
|---|---|
| 1. Aldol condensation                     | 25. Sandmeyer reaction                        |
| 2. Claisen-Schmidt reaction               | 26. Ullmann reaction                          |
| 3. Knoevenagel condensation               | 27. Wurtz reaction                            |
| 4. Perkin's condensation                  | 28. Wurtz-Fittig synthesis                    |
| 5. Cannizzaro reaction                    | 29. Clemmensen reduction                      |
| 6. Tishchenko reaction                    | 30. Rosenmund reduction                       |
| 7. Benzoin condensation                   | 31. Wolff-Kishner reduction                   |
| 8. Claisen condensation                   | 32. Kolbe's electrolysis                      |
| 9. Michael condensation                   | 33. Selenium dioxide oxidation                |
| 10. Dieckmann condensation                | 34. Bouveault synthesis of aldehydes          |
| 11. Thorpe's reaction                     | 35. Reimer-Tiemann reaction                   |
| 12. Acetoacetic ester synthesis           | 36. Hoesch reaction                           |
| 13. Malonic ester synthesis               | 37. Friedel-Crafts reaction                   |
| 14. Hofmann's exhaustive methylation      | 38. Reformatsky reaction                      |
| 15. Hofmann's hypobromite reaction        | 39. Grignard methods                          |
| 16. Gabriel's synthesis                   | 40. Ozonolysis                                |
| 17. Hinsberg reaction                     | 41. Hydrogenation                             |
| 18. Strecker's reaction                   | 42. Hydrogenolysis                            |
| 19. The modified Strecker reaction        | 43. Diels-Alder reaction                      |
| 20. Von Braun's cyanogen bromide reaction | 44. Schotten-Baumann reaction                 |
| 21. Diazotization                         | 45. Transesterification                       |
| 22. Coupling reaction                     | 46. Skraup reaction                           |
| 23. Gattermann reaction                   | 47. Kolbe's synthesis of hydroxybenzoic acids |
| 24. Gattermann-Koch reaction              | 48. Williamson's synthesis                    |
|   | 49. Polymerization                            |

- |                         |                                    |
|-------------------------|------------------------------------|
| 50. Hydrolysis          | 57. Acetal formation               |
| 51. Saponification      | 58. Autoxidation                   |
| 52. Dehydration         | 59. Halogenation                   |
| 53. Cyclodehydration    | 60. Hell-Volhard-Zelinsky reaction |
| 54. Dehydrogenation     | 61. Nitration                      |
| 55. Dehydrohalogenation | 62. Sulfonation                    |
| 56. Haloform reaction   |                                    |

III. Define and illustrate the following terms:

- |                               |                   |
|-------------------------------|-------------------|
| 1. <i>cis-trans</i> Isomerism | 11. Mercaptol     |
| 2. Walden inversion           | 12. Alkaloid      |
| 3. Chromophore group          | 13. Lactol        |
| 4. Glycoside                  | 14. Lactam        |
| 5. Acetal                     | 15. Diazotization |
| 6. Aromaticity                | 16. Ketopentose   |
| 7. Polymer                    | 17. Terpene       |
| 8. Fulvene                    | 18. Mordant dye   |
| 9. Free radical               | 19. Ketene        |
| 10. Quinhydrone               | 20. Sulfone       |

IV. Illustrate the following types of molecular rearrangements:

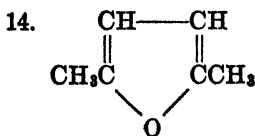
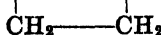
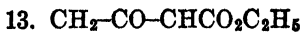
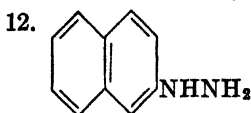
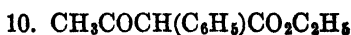
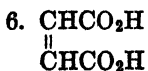
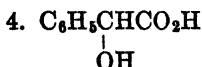
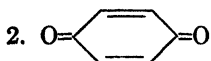
- |                  |                       |
|------------------|-----------------------|
| 1. Allylic       | 8. Jacobsen           |
| 2. Hofmann (2)   | 9. Pinacol-pinacolone |
| 3. Fischer-Hepp  | 10. Curtius           |
| 4. Benzidine     | 11. Claisen           |
| 5. Benzilic acid | 12. Beckmann          |
| 6. Demjanow      | 13. Lossen            |
| 7. Fries         | 14. Enolization       |

V. Discuss the use of the following reagents in organic chemistry:

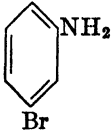
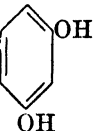
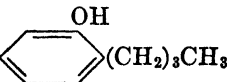
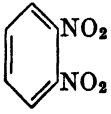
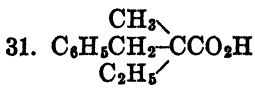
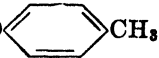
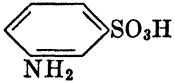
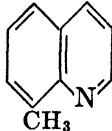
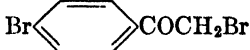
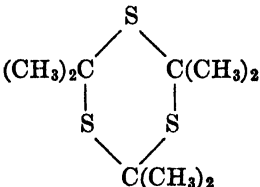
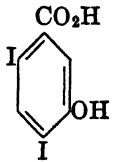
- |                             |                       |
|-----------------------------|-----------------------|
| 1. Acetic anhydride         | 16. Chromic anhydride |
| 2. Acetyl chloride          | 17. Copper            |
| 3. Aluminum amalgam         | 18. Copper-bronze     |
| 4. Aluminum chloride        | 19. Copper sulfate    |
| 5. Aluminum isopropoxide    | 20. Cuprous chloride  |
| 6. Ammonium chloride        | 21. Cuprous cyanide   |
| 7. Ammonium sulfide         | 22. Diazomethane      |
| 8. Barium hydroxide         | 23. Ferric chloride   |
| 9. Benzenesulfonyl chloride | 24. Hydrogen          |
| 10. Benzoyl peroxide        | 25. Hydrogen chloride |
| 11. Boron trifluoride       | 26. Hydrogen cyanide  |
| 12. Bromine                 | 27. Hydrogen iodide   |
| 13. Calcium hydroxide       | 28. Hydrogen peroxide |
| 14. Chlorine                | 29. Hydroxylamine     |
| 15. Chlorosulfonic acid     | 30. Iodine            |
|                             | 31. Iron              |

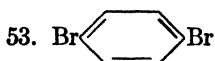
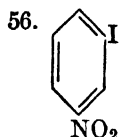
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|--|-------------------------|
| 32. Magnesium amalgam                  | 57. Semicarbazide       |
| 33. Maleic anhydride                   | 58. Silver              |
| 34. Mercuric acetate                   | 59. Silver nitrate      |
| 35. Methyl sulfate                     | 60. Silver oxide        |
| 36. Nickel                             | 61. Sodium              |
| 37. Nitric acid                        | 62. Sodium acetate      |
| 38. Nitrous acid                       | 63. Sodium amalgam      |
| 39. Oxygen                             | 64. Sodium amide        |
| 40. Ozone                              | 65. Sodium bisulfite    |
| 41. Palladium                          | 66. Sodium dichromate   |
| 42. Phenylhydrazine                    | 67. Sodium ethoxide     |
| 43. Phenyl isocyanate                  | 68. Sodium hydroxide    |
| 44. Phosphorus oxychloride             | 69. Sodium hypochlorite |
| 45. Phosphorus pentabromide            | 70. Sodium iodide       |
| 46. Phosphorus pentachloride           | 71. Sodium nitrite      |
| 47. Phosphorus pentoxide               | 72. Sodium sulfite      |
| 48. Phosphorus trichloride             | 73. Stannic chloride    |
| 49. Picric acid                        | 74. Stannous chloride   |
| 50. Piperidine                         | 75. Sulfur              |
| 51. Platinum                           | 76. Sulfur dioxide      |
| 52. Potassium cyanide                  | 77. Sulfuric acid       |
| 53. Potassium hydroxide<br>(alcoholic) | 78. Thionyl chloride    |
| 54. Potassium permanganate             | 79. Tin                 |
| 55. Selenium                           | 80. Zinc                |
| 56. Selenium dioxide                   | 81. Zinc chloride       |
|  | 82. Zinc cyanide        |

VI. Outline satisfactory methods for making the following compounds from readily available raw materials. Indicate the catalysts used and classify the condensation reactions which are involved.

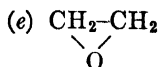
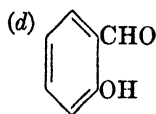
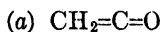




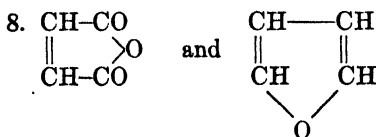
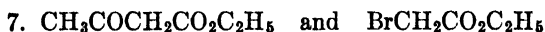
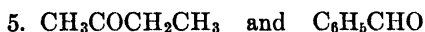
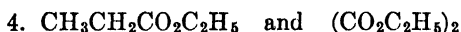
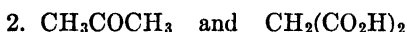
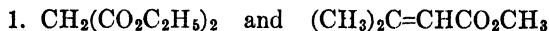
15.  $\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_3$
16.  $\text{CH}_3\text{CHCO}_2\text{C}_2\text{H}_5$   
 $\quad \quad \quad \text{COCO}_2\text{C}_2\text{H}_5$
17.  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$
18.  $(\text{CH}_3)_2\text{C}=\text{CHCO}_2\text{H}$
19.  $(\text{CH}_3)_2\text{C}(\text{OH})\text{CO}_2\text{C}_2\text{H}_5$
20. 
21.  $\text{CH}_3\text{COCHCO}_2\text{C}_2\text{H}_5$   
 $\quad \quad \quad \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$
22.  $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}=\text{CHC}_6\text{H}_5$
23. 
24.  $p\text{-CH}_3\text{C}_6\text{H}_4\text{CHO}$
25.  $(\text{C}_2\text{H}_5\text{O}_2\text{C})_2\text{C}=\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2$
26. 
27.  $\text{HO}_2\text{C}(\text{CH}_2)_5\text{CO}_2\text{H}$
28.  $\text{C}_6\text{H}_5\text{CH}(\text{CN})\text{CH}_2\text{COC}_6\text{H}_5$
29. 
30.  $\text{CH}_3\text{COCH}(\text{CH}_3)\text{CHCOCH}_3$   
 $\quad \quad \quad \text{CH}_3 \quad \text{CH}_3$
31. 
32.  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CO}_2\text{H}$
33.  $\text{CH}_3\text{NO}_2$
34.  $\text{C}_6\text{H}_5\text{SH}$
35.  $\text{C}_6\text{H}_5\text{CO}$  
36. 
37.  $\text{CH}_2=\text{CH}-\underset{\text{Cl}}{\text{C}}=\text{CH}_2$
38. 
39. 
40.  $\text{CH}_2-\underset{\text{CH}_2-\text{CH}_2}{\text{CHCO}_2\text{H}}$
41. 
42.  $\text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_5$
43.  $\text{CH}_2=\text{CHOCOCH}_3$
44.  $\text{CH}_3\text{NHC}_2\text{H}_5$
45.  $\text{CH}_2=\underset{\text{CH}_3}{\text{CCO}_2\text{CH}_3}$
46. 
47.  $\text{CH}_2=\text{CHCl}$
48.  $\text{CH}_3\text{CH}_2\text{SO}_3\text{H}$



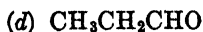
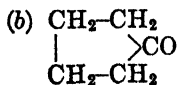
VII. Show by equations what happens when phenylmagnesium bromide is treated with a limited amount of



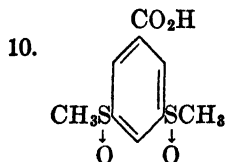
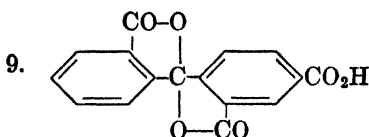
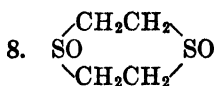
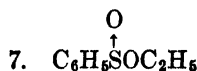
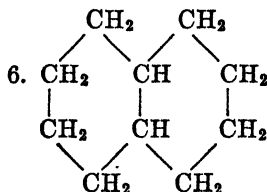
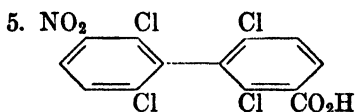
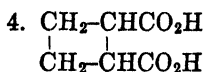
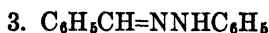
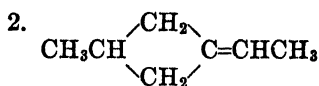
VIII. For each of the following pairs of compounds indicate a useful reaction which may be caused to take place, and mention any catalysts which may be involved:



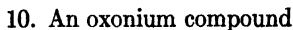
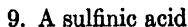
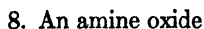
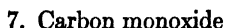
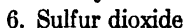
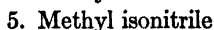
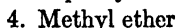
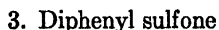
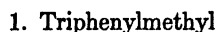
IX. Arrange the following compounds in a decreasing order of reactivity toward methylmagnesium iodide:



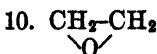
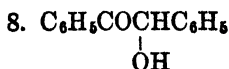
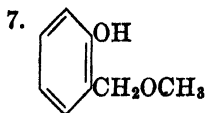
X. Indicate the number and type of stereoisomers possible for the following structures:

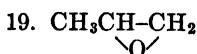
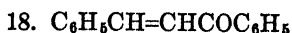
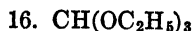
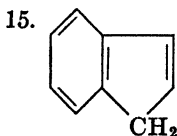


XI. Write electronic formulas for the following compounds:

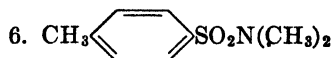
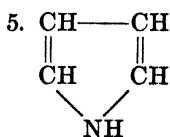
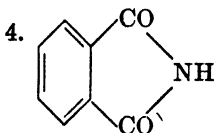
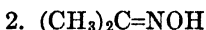


XII. Show what occurs when the following compounds react with an excess of ethylmagnesium bromide. In each case write the formula of the principal product obtained when the condensation product is treated with dilute sulfuric acid.





XIII. Compare the basic strengths of the following nitrogen compounds:



XIV. (a) Discuss the reduction of nitro compounds.

(b) What types of compounds are colored?

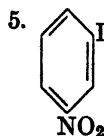
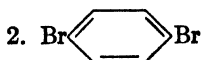
(c) What is a dye? Give several types.

(d) Why is the coupling of diazonium salts carried out in alkaline media?

(e) Compare the chemical reactions of primary amines ( $\text{RNH}_2$ ) and simple amides ( $\text{RCONH}_2$ ).

(f) In what types of nitro compounds is the nitro group replaceable?

XV. Arrange the following halogen compounds in a decreasing order of reactivity toward silver nitrate. Which of these compounds will yield a Grignard reagent?





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